THE

AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

JULY, 1937

ORIGINAL ARTICLES.

INTENSIVE COLLAPSE THERAPY IN PULMONARY TUBERCULOSIS.

II. A Study of the Indications and Use of Various Operative Procedures in a Group of 1124 Patients.

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The history of tuberculosis almost automatically divides itself into three phases, the last two of which have been initiated by revolutionary changes in therapeutic methods. The first phase was centuries long, characterized by a sense of futility and resignation toward the disease, and so far as treatment is concerned, chiefly by the mere palliative management of the outstanding symptoms. It almost abruptly merged, only a few decades ago, into the "rest-cure" conception of management. In its turn this second phase, by virtue of accumulated knowledge concerning the pathology and behavior of the disease under such a regimen, provides an important background and indispensable working adjunct for the therapeutic revolution that has within comparatively recent years initiated the third phase, namely the development of the various methods of thoracic surgery. We except pneumothorax therapy from this latter classification, since it is not strictly a surgical development. However, this by no means minimizes its importance, since it has been a concomitant of both the second and third phase of tuberculosis progress, and its influence on the development of the later purely surgical methods is universally recognized. Pneumothorax remains today probably the most important single therapeutic measure available to us.

The evolution of collapse therapy still progresses, not only in the refinements of the various methods employed, but also in the continually widening concept by phthisiotherapists of the possibilities that lie in the extended clinical use of these procedures. This radical change in the perception of the possibilities of treatment, encouraged by the excellent final results of treatment being reported, finds expression in the present attitude toward bilateral disease, toward which we have lost most of our recent pessimism. Bilateral cavities are today attacked with almost as much confidence as marked the application of pneumothorax therapy to unilateral disease only a few years ago.

In a recent paper[3] in this journal we gave in some detail the final results of treatment of a series of 1124 patients with the adult type of pulmonary tuberculosis consecutively admitted to this sanatorium between June 1, 1930, and June 30, 1934, of whom nearly 80% had one or more collapse therapy operations. The results provided an excellent justification of this apparently high percentage use of such therapy: Of 823 discharged patients, the tuberculosis of 47.3% of the entire group and 55.4% of those surgically treated, became arrested or apparently arrested; favorable results (improved to arrested), were 67.1% and 77.8% respectively; in the entire group of 1124 patients (78.8% of whom had surgical treatment), cavity closure was effected in 61.2% of all cases with cavity, and in 71.5% of the surgically treated cavity cases; sputum conversion was effected in 61.9% of all patients with positive sputum, and in 71.8% of those surgically treated.

An adequate analysis of any therapeutic program is necessary for its proper evaluation and an appreciation of the results of treatment. The tables presented in this article attempt to give a somewhat detailed analysis of the indications and actual use of the various methods of collapse therapy employed in this large series of patients. These statistics are closely identified, classification for classification, with the results of treatment previously reported, and, except for lack of space, would properly have been published in the same article. A comparison of the tables in the two articles at once makes apparent the amount and character of the collapse therapy that was responsible for certain results in corresponding small group-subdivisions of the entire series of patients.

Interpretation of Tables. Each of the first three tables, similarly arranged, gives, in the first two columns under each diagnostic classification, the number of patients under treatment for more than 6 months and for less than 6 months, respectively, who received a certain operation or combination of operations (see operation code under Table 1). The fifth and sixth columns in the same section indicate the total number of operations performed for that group of patients. Here the duplication of operations becomes evident. For example, in the third line of Table 1, fourth section, it will be seen that 224 phrenic operations were performed on 182 patients who were treated for more than 6 months, and that these patients also

received pneumothorax therapy, 10 having had bilateral pneumothorax. It is also seen that one patient received a scaleniectomy in addition to pneumothorax and phrenic surgery, and that another had a multiple intercostal neurectomy operation. It was necessary, throughout the tables, to insert in this way the code for scaleniectomy and intercostal neurectomy, since the addition of sections to the tables for these operations in their proper combinations with the five more important procedures would have made the tables impossibly cumbersome. For the same reason oleothorax is considered separately in the text. However, in order to avoid confusion, percentage figures in Columns 3 and 4 are based strictly upon combination of the five procedures at the left of the table. The inserted operations are so few in number, relatively, as to cause no important change in the percentages. Column 3 in the same section of Table 1 indicates that 32.6% of the 595 surgically treated patients received the combination of artificial pneumothorax and phrenic surgery, and Column 4 indicates that 23.6% of the 823 combined surgically and non-surgically treated patients received these two procedures.

Table 4, in summary, presents a percentage compilation of the various individual procedures, and indicates their relative importance in the therapeutic program. No comparison between the proportions of collapse therapy for male or female patients has been made, nor has any study been made of the application of collapse therapy by age groups, although such figures would be interesting. Approximately 12% of the discharged patients were more than 40 years old, and less than 4% were more than 50.

Collapse Therapy in Discharged Patient Group (Table 1). The subheadings of this table indicate the percentage of the minimal, moderately advanced and far advanced patients who had collapse therapy before discharge. The corresponding results of this treatment, as indicated by the condition of these 595 patients at the time of discharge, may be obtained by referring to Section 1 of Table 1 of the previous report.[3] It is interesting to note that, of the 39 minimal cases which received collapse therapy, none received pneumothorax alone, although 36 had phrenic surgery alone, and 3 had the two procedures combined. It is quite apparent that more than half of the 90 minimal patients discharged were thought to be in such satisfactory control of their lesion as not to require collapse therapy during their hospital stay and, furthermore, that phrenic surgery and pneumothorax for the remainder apparently forestalled the development of complications that might have required more risky surgical methods. Since 1934, however, nearly 90% of the minimal cases admitted have received collapse therapy, in contrast with the 43.4% of this report.

It will be noted that, of the 215 discharged moderately advanced cases which received collapse therapy in some form, phrenic surgery was apparently the only treatment considered necessary for 53.9%, with the exception that one of the 116 patients comprising this therapy group had a multiple intercostal neurectomy, and 2 others a scaleniectomy. Pneumothorax alone, and combined pneumothorax and phrenic surgery, were used for 76 patients, leaving only 23 patients, or 10.8% of the 215 surgically treated moderately advanced cases, for whom more advanced surgery was prescribed.

TABLE 1.—CLASSIFICATION OF VARIOUS OPERATIONS USED FOR 595 DISCHARGED PATIENTS.

	Minimal (39 of 90).						Moderately advanced (215 of 263).						Far advanced (341 of 470).						Combined (595 of 823).					
	Cases.				Operations.		Cases.				Operations.		Cases.				Operations.		Cases.				Operations.	
	Over 6 mos.	Under 6 mos.	Per cent of 39 surgical.	Per cent of total.	Over 6 mos.	Under 6 mos.	Over 6 mos.	Under 6 mos.	Per cent of 215 surgical.	Per cent of total.	Over 6 mos.	Under 6 mos.	Over 6 mos.	Under 6 mos.	Per cent of 341 surgical.	Per cent of total.	Over 6 mos.	Under 6 mos.	Over 6 mos.	Under 6 mos.	Per cent of 595 surgical.	Per cent of total.	Over 6 mos.	Under 6 mos.
Pneumothorax	—	—	—	—	—	—	10	—	4 6	3 8	10Px	—	45	11	16 4	11 9	*10Px 35Px	11Px	55	11	11 1	8 0	*10Px* 45Px	11Px
Phrenic surgery	32	4	92 3	40 0	46Ph	4Ph	97	19	53 9	44 1	1IN 117Ph	2Sc 20Ph	55	3	17 0	12 4	1IN 64Ph	4Ph	184	26	35 3	25 5	2IN 227Ph	2Sc 28Ph
Pneumothorax Phrenic surgery	3	—	7 7	3 4	3Px 3Ph	—	62	4	30 7	25 1	*1Px 61Px 89Ph	4Px 4Ph	117	8	36 6	26 6	1Sc 1IN *9Px 108Px 132Ph	*1Px 7Px 8Ph	182	12	32 6	23 6	1Sc 1IN *10Px 172Px 241Ph	*1Px 11Px 12Ph
Pneumothorax Intrapl. pn'lysis	—	—	—	—	—	—	3	—	1 4	1 1	3Px 3IP	—	7	3	2 9	2 1	7Px 8IP	3Px 3IP	10	3	2 2	1 6	10Px 11IP	3Px 3IP
Pneumothorax Phrenic surgery Intrapl. pn'lysis	—	—	—	—	—	—	3	—	1 4	1 1	3Px 4Ph 3IP	—	17	1	5 3	3 8	1Sc *2Px 15Px 22Ph 19IP	1Px 1Ph 1IP	20	1	3 6	2 6	1Sc *2Px 18Px 26Ph 22IP	1Px 1Ph 1IP
Pneumothorax Extrapl. pn'lysis	—	—	—	—	—	—	—	—	—	—	—	—	2	—	0 6	0 4	*1Px 1Px 2EP	—	2	—	0 3	0 2	*1Px 1Px 2EP	—
Pneumothorax Phrenic surgery Extrapl. pn'lysis	—	—	—	—	—	—	1	—	0 5	0 4	1Px 1Ph 1EP	—	2	—	0 6	0 4	2Px 3Ph 2EP	—	3	—	0 5	0 4	3Px 4Ph 3EP	
Phrenic surgery Extrapl. pn'lysis	—	—	—	—	—	—	5	1	2 8	2 3	1Sc 5Ph 7EP	1Ph 1EP	10	—	2 9	2 1	1Sc 11Ph 12EP	—	15	1	2 7	1 9	2Sc 16Ph 19EP	1Ph 1EP

Extrapl. pn'lysis	—	—	—	—	—	—	2	—	0.9	0.8	2EP	—	3	—	0.9	0.7	5EP	—	5	—	0.8	0.6	7EP	
Pneumothorax Thoracoplasty	—	—	—	—	—	—	—	—	—	—	—	—	2	—	0.6	0.4	2Px 7Th	—	2	—	0.3	0.2	2Px 7Th	
Pneumothorax Phrenic surgery Thoracoplasty	—	—	—	—	—	—	4	—	1.9	1.5	4Px 4Ph 12Th	—	27	—	7.9	5.7	1Sc 1IN *2Px 25Px 30Ph 82Th	—	31	—	5.2	3.8	1Sc 1IN *2Px 29Px 34Ph 94Th	—
Pneumothorax Phrenic surgery Intrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	—	—	—	—	—	—	3	—	0.9	0.7	3Px 4Ph 4IP 17Th	—	3	—	0.5	0.4	3Px 4Ph 4IP 17Th	—
Pneumothorax Phrenic surgery Extrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	—	—	—	—	—	—	5	—	1.5	1.1	*1Px 4Px 7Ph 7EP 7Th	—	5	—	0.8	0.6	*1Px 4Px 7Ph 7EP 7Th	—
Phrenic surgery Extrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	—	—	—	—	—	—	4	—	1.2	0.9	4Ph 4EP 9Th	—	4	—	0.7	0.5	4Ph 4EP 9Th	—
Phrenic surgery Thoracoplasty	—	—	—	—	—	—	2	—	0.9	0.8	2Sc 2Ph 7Th	—	11	3	4.1	3.0	2IN 13Ph 29Th	3Ph 6Th	13	3	2.7	1.9	2Sc 2IN 15Ph 36Th	3Ph 6Th
Extrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	1	—	0.5	0.4	1EP 3Th	—	—	—	—	—	—	—	—	1	—	0.2	0.1	1EP 3Th	—
Thoracoplasty	—	—	—	—	—	—	1	—	0.5	0.4	2Th	—	1	1	0.6	0.4	3Th	3Th	2	1	0.5	0.4	5Th	3Th
Totals	35	4	100.0	43.4	3Px 49Ph	4Ph	191	24	100.0	81.8	†3Sc †1IN *1Px 82Px 222Ph 6IP 11EP 24Th	†2Sc 4Px 25Ph 1EP	311	30	100.0	72.6	†4Sc †5IN *25Px 202Px 290Ph 31IP 32EP 154Th	*1Px 22Px 16Ph 4IP 9Th	537	58	100.0	72.3	†7Sc †6IN *26Px 287Px 561Ph 37IP 43EP 178Th	†2Sc *1Px 26Px 45Ph 4IP 1EP 9Th

In Columns 5 and 6 of each section, the code letters are interpreted as follows: Px = Pneumothorax, Ph = Phrenic Surgery IP = Intrapleural Pneumonolysis, EP = Extrapleural Pneumonolysis, Th = Thoracoplasty, Sc = Scaleniectomy, IN = Intercostal Neurectomy,

* Wherever used in the table indicates bilateral pneumothorax.

† Intercostal Neurectomy (IN) and Scaleniectomy (Sc) are treated as inserts in Columns 5 and 6 of each section and are not classified at the left of the table, and the number preceding the code letters indicates the number of patients rather than the number of operations.

These figures also apparently attest to the value of phrenic surgery and artificial pneumothorax, if performed without delay after the admission of the patient, in forestalling further development of the disease. The 23 patients who required more extensive surgery are divided (Section 2, Table 1) into 9 different groups according to the operative procedures performed singly or in sequence. Phrenic surgery was combined with extrapleural pneumonolysis with paraffin plombage for 3 of the 23 (1 patient also had a scaleniectomy). Thoracoplasty operations were performed for 8 of the 23 patients, in 1 instance alone, and for 7 patients combined with one or more other procedures. Another rather significant fact is that, while 87 of these 215 patients had pneumothorax therapy, only 6 required the intrapleural division of adhesions which prevented an effective collapse of the lung. As this operation was necessary in less than 7% of the moderately advanced pneumothorax cases, while it was necessary in 12.4% of the far advanced cases with pneumothorax, it is quite apparent that these figures corroborate the general belief that the development of pleural symphysis tends to parallel the progressive development of the pulmonary disease. Further evidence is furnished by the fact that in the moderately advanced group only 16.3% of attempted pneumothoraces resulted in failure to induce a satisfactory collapse, as compared with 27.3% in the far advanced group.

As compared with the former group, a marked change is noted in the character of the treatment given to the 341 far advanced surgically treated cases. Only 17%, as compared with 53.9% for the moderately advanced group, were subjected to phrenic surgery alone (1 case also received intercostal neurectomy). Pneumothorax alone, and combined pneumothorax and phrenic surgery, were prescribed for 53% of the group, as compared with 35.3% of the moderately advanced group. This leaves 102 patients, or 30%, as compared with 10.8%, for whom more drastic surgical measures were found necessary to supplement these two procedures. Approximately 56% of these had thoracoplasty operations, alone in 2 instances, and in combination with one or more other procedures in 55 patients. Extrapleural paraffin plombage was resorted to in approximately one-fourth (25.5%) of this major-surgery group of 102. In 3 instances this was the only operation, and in 9 instances it was performed in conjunction with thoracoplastic surgery; in this connection plombage and thoracoplasty were either used on opposite sides, or occasionally the thoracoplasty was a supplementary operation on the same side when plombage failed to close completely the pulmonary cavity.

(It should be explained that, where major surgery such as thoracoplasty is the only procedure listed, pneumothorax therapy has almost invariably been unsuccessfully attempted. Statistics for these failures are not tabulated.)

The combined figures for the entire group of 823 discharged patients (Section 4, Table 1) would seem to indicate that in the average large group of patients subjected to intensive collapse therapy, and for whom treatment has been completed, approximately one-fourth of the group will require nothing more than phrenic surgery; that artificial pneumothorax will have been used, for the most part in conjunction with other procedures, for more than 40% of all patients (being indicated, if unsuccessful attempts to induce pneumothorax are included, in approximately 50% of patients); that extrapleural thoracoplasty will be indicated in about 8% of all patients; and that approximately 15% of such an average group of patients will require major thoracic surgery.

Collapse Therapy in Resident-patient Group (Table 2). The reason for the extremely high percentage of collapse therapy in this group (291 patients, or 96.7%), is explained by the fact that, while no patients were included in this study who were admitted after June 30, 1934, the statistics for resident patients were obtained as of January 1, 1935. Therefore all these patients had at least 6 months' treatment. All patients admitted up to June 30, 1934, who had less than 6 months' treatment, automatically fall into the discharged group (Table 1), including all patients discharged during the 6 months previous to January 1, 1935.

From this figure (96.7%) we can therefore draw a significant inference. Collapse therapy is either immediately or eventually indicated for practically 100% of all patients who remain in a sanatorium for at least 6 months. The small group of slightly more than 3% who were not under such therapy includes 2 minimal cases, and 4 far advanced terminal cases who lingered beyond expectation.

For this reason, a comparison of the use of surgical methods in this group with those in the discharge group would not be equitable. The resident group would naturally include a much larger proportion of the more unstable lesions. This is apparently shown in Sections 1 and 2 of Table 2. Nearly 31% of the 13 minimal cases under collapse therapy required pneumothorax as an adjunct to phrenic surgery, as compared with less than 8% of the 39 discharged minimal cases. In the moderately advanced resident group, 29.7% of the surgically treated patients required more operative aid than pneumothorax or phrenic surgery could give them, as compared with 10.8% in the discharge group. The corresponding figures for the far advanced cases requiring more advanced surgery are 44.5% as compared with 30%. It will be noted that in the resident group thoracoplasty plays a much more important part (Section 4, Table 2). Nearly 18% of the 291 surgically treated resident patients required thoracoplasty, as compared with 11% of the discharged patients. It must also be remembered that this resident group will probably require more surgery before discharge marks the end of treatment.

TABLE 2.—CLASSIFICATION OF VARIOUS OPERATIONS USED FOR 291 RESIDENT PATIENTS.

	Minimal (13 of 15).				Moderately advanced (98 of 102).				Far advanced (180 of 184).				Combined (291 of 301).			
	Cases.	Per cent of 13 surgical.	Per cent of total.	Operations.	Cases.	Per cent of 98 surgical.	Per cent of total.	Operations.	Cases.	Per cent of 180 surgical.	Per cent of total.	Operations.	Cases.	Per cent of 291 surgical.	Per cent of total.	Operations.
Pneumothorax	—	—	—	—	12	12.2	11.8	*3Px 9Px	15	8.3	8.2	*5Px 10Px	27	9.3	9.0	*8Px 19Px
Phrenic surgery	9	69.2	60.0	17Ph	30	30.6	29.4	1Sc 1IN 48Ph	22	12.2	12.0	2Sc 5IN 29Ph	61	21.0	20.3	3Sc 6IN 94Ph
Pneumothorax Phrenic surgery	4	30.8	26.7	4Px 4Ph	27	27.5	26.5	1Sc 1IN *4Px 23Px 36Ph	63	35.0	34.2	2Sc *23Px 40Px 75Ph	94	32.3	31.2	3Sc 1IN *27Px 67Px 115Ph
Pneumothorax Intrapl. pn'lysis	—	—	—	—	2	2.0	2.0	*1Px 1Px 2IP	9	5.0	4.9	*4Px 5Px 10IP	11	3.8	3.7	*5Px 6Px 12IP
Pneumothorax Intrapl. pn'lysis Phrenic surgery	—	—	—	—	8	8.2	7.9	8Px 10Ph 8IP	21	11.6	11.4	*8Px 13Px 30Ph 27IP	29	10.0	9.6	*8Px 21Px 40Ph 35IP
Pneumothorax Phrenic surgery Extrapl. pn'lysis	—	—	—	—	3	3.1	2.9	1Sc 3Px 3Ph 4EP	2	1.1	1.1	*1Px 1Px 2Ph 3EP	5	1.7	1.7	1Sc *1Px 4Px 5Ph 7EP
Pneumothorax Phrenic surgery Intrapl. pn'lysis Extrapl. pn'lysis	—	—	—	—	—	—	—	—	1	0.6	0.5	*1Px 1Ph 1IP 1EP	1	0.3	0.3	1Px 1Ph 1IP 1EP
Phrenic surgery Extrapl. pn'lysis	—	—	—	—	3	3.1	2.9	5Ph 4EP	8	4.4	4.4	1Sc 13Ph 9EP	11	3.8	3.7	1Sc 18Ph 13EP
Extrapl. pn'lysis	—	—	—	—	1	1.0	1.0	1EP	—	—	—	—	1	0.3	0.3	1EP
Pneumothorax Thoracoplasty	—	—	—	—	—	—	—	—	3	1.7	1.6	3Px 10Th	3	1.0	1.0	3Px 10Th
Pneumothorax Phrenic surgery Thoracoplasty	—	—	—	—	6	6.1	5.9	1Sc *1Px 5Px 8Ph 18Th	24	13.3	13.1	2Sc 1IN *6Px 18Px 25Ph 77Th	30	10.3	10.0	3Sc 1IN *7Px 23Px 33Ph 95Th
Pneumothorax Intrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	—	—	1	0.6	0.5	*1Px 2IP 5Th	1	0.3	0.3	*1Px 2IP 5Th
Pneumothorax Phrenic surgery Intrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	—	—	1	0.6	0.5	1Px 1Ph 1IP 5Th	1	0.3	0.3	1Px 1Ph 1IP 5Th
Phrenic surgery Extrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	—	—	2	1.1	1.1	2Ph 2EP 5Th	2	0.7	0.7	2Ph 2EP 5Th
Phrenic surgery Thoracoplasty	—	—	—	—	3	3.1	2.9	1IN 3Ph 9Th	7	3.9	3.8	9Ph 34Th	10	3.5	3.3	1IN 12Ph 43Th
Thoracoplasty	—	—	—	—	3	3.1	2.9	7Th	1	0.6	0.5	4Th	4	1.4	1.3	11Th
Totals	13	100.0	86.7	4Px 21Ph	98	100.0	96.1	†8Sc †3IN *9Px 49Px 113Ph 10IP 9EP 34Th	180	100.0	97.8	†7Sc †6IN *49Px 91Px 187Ph 4IP 15EP 140Th	291	100.0	96.7	†11Sc †9IN *58Px 144Px 321Ph 5IP 24EP 174Th

In Column 4 of each section, the code letters are interpreted as follows: Px = Pneumothorax, Ph = Phrenic surgery, IP = Intrapleural pneumonolysis, EP = Extrapleural pneumonolysis, Th = Thoracoplasty, Sc = Scaleniectomy, IN = Intercostal neurectomy.

* Wherever used in the table indicates bilateral pneumothorax.

† Intercostal neurectomy (IN) and Scaleniectomy (Sc) are treated as inserts in Column 4 of each section and are not classified at the left of the table, and the number preceding the code letters indicates the number of patients rather than the number of operations.

Collapse Therapy in the Entire Group of 1124 (Table 3). Most of the important points covered in the previous discussion apply here, with less change than is noted in comparison between Tables 1 and 2. However, we think it is important to emphasize certain points with exact percentage figures because the statistics in Table 3 are those detailing the treatment given a complete consecutively admitted patient group.

Apparently phrenic surgery (not necessarily permanent paralysis) is all that is necessary for seven-eighths (86.6%, Section 1) of the surgically treated minimal cases admitted to a sanatorium. In our complete study group, not one minimal case required anything other than phrenic surgery or pneumothorax. Since these measures were prescribed whenever there was the least roentgenologic or symptomatic evidence of active disease, we regard these figures (Section 1, Table 3) as proof of the value of such a treatment policy, in forestalling possible unfavorable developments. Incidentally, none of these patients died, in 72.2% the disease was arrested or apparently arrested, and the remainder were either discharged against advice or were permitted to go home because their excellent condition did not justify keeping them long enough to qualify under the National Tuberculosis Association standards for "apparent arrest."

Of the entire number of surgically treated patients (886, or 78.8% of the whole), pneumothorax was the only treatment used for 10.5%, phrenic surgery alone for 30.6%, and the combined procedures for 32.5%. There were, however, 10 of the phrenic surgery group of 271, and 6 of the combined pneumothorax and phrenic surgery group of 288 who had, in addition to these procedures, a scaleniectomy or multiple intercostal neurectomy. A total, therefore, of 250 patients (28.2% of the surgical group) required major surgery.

Extrapleural thoracoplasty, either alone (7 cases) or in various combinations with other procedures, was performed for 116 of these patients; this represents 46.4% of the major surgery group, 13.1% of the entire surgical group, and 10.3% of the entire series of patients. Extrapleural pneumonolysis with plombage was performed alone in 6 of this major surgery group, and with other procedures in a total of 56 patients, which represents 5% of the entire series, and 22.4% of the major surgery group. The intrapleural division of adhesions for unsatisfactory pneumothorax collapse was necessary in 80 patients, representing 32% of the major surgery group, 9% of the entire surgical group, and 7.1% of all patients studied.

Considering the whole group of 1124 patients, another significant fact is obvious from a study of Table 3 (Column 4, Section 4). Only one-twelfth (8.3%) of all patients had pneumothorax therapy alone. Therefore approximately 70% of all the patients admitted to the sanatorium had one or more actual surgical operations other than

TABLE 3.—CLASSIFICATION OF VARIOUS OPERATIONS USED FOR 886 PATIENTS

	Minimal (52 of 105).						Moderately advanced (313 of 365).						Far advanced (521 of 654).						Combined (886 of 1124).					
	Cases.				Operations.		Cases.				Operations.		Cases.				Operations.		Cases.				Operations.	
	Over 6 mos.	Under 6 mos.	Per cent of 52 surgical.	Per cent of total.	Over 6 mos.	Under 6 mos.	Over 6 mos.	Under 6 mos.	Per cent of 313 surgical.	Per cent of total.	Over 6 mos.	Under 6 mos.	Over 6 mos.	Under 6 mos.	Per cent of 521 surgical.	Per cent of total.	Over 6 mos.	Under 6 mos.	Over 6 mos.	Under 6 mos.	Per cent of 886 surgical.	Per cent of total.	Over 6 mos.	Under 6 mos.
Pneumothorax	—	—	—	—	—	—	22	—	7.0	6.0	*3Px 19Px	—	60	11	13.6	10.9	*15Px 45Px	11Px	82	11	10.5	8.3	*18Px 64Px	11Px
Phrenic surgery	41	4	86.6	42.8	63Ph	4Ph	127	19	46.6	40.0	1Sc 2IN 165Ph	2Sc 20Ph	77	3	15.3	12.2	2Sc 6IN 93Ph	4Ph	245	26	30.6	24.1	3Sc 8IN 321Ph	2Sc 28Ph
Pneumothorax Phrenic surgery	7	—	13.4	6.7	7Px 7Ph	—	89	4	29.7	25.5	1Sc 1IN *5Px 84Px 125Ph	4Px 4Ph	180	8	36.1	28.7	3Sc 1IN *32Px 148Px 207Ph	*1Px 7Px 8Ph	276	12	32.5	25.6	4Sc 2IN *37Px 239Px 339Ph	*1Px 11Px 12Ph
Pneumothorax Intrapl. pn'lysis	—	—	—	—	—	—	5	—	1.6	1.4	*1Px 4Px 5IP	—	16	3	3.6	2.9	*4Px 12Px 18IP	3Px 3IP	21	3	2.7	2.1	*5Px 16Px 23IP	3Px 3IP
Pneumothorax Intrapl. pn'lysis Phrenic surgery	—	—	—	—	—	—	11	—	3.5	3.0	11Px 14Ph 11IP	—	38	1	7.5	5.9	1Sc *10Px 28Px 52Ph 46IP	1Px 1Ph 1IP	49	1	5.6	4.4	1Sc *10Px 39Px 66Ph 57IP	1Px 1Ph 1IP
Pneumothorax Extrapl. pn'lysis	—	—	—	—	—	—	—	—	—	—	—	—	2	—	0.4	0.3	*1Px 1Px 2EP	—	2	—	0.2	0.2	*1Px 1Px 2EP	—
Pneumothorax Phrenic surgery Extrapl. pn'lysis	—	—	—	—	—	—	4	—	1.3	1.1	1Sc 4Px 4Ph 5EP	—	4	—	0.8	0.6	*1Px 3Px 5Ph 5EP	—	8	—	0.9	0.7	1Sc *1Px 7Px 9Ph 10EP	—
Pneumothorax Phrenic surgery Intrapl. pn'lysis Extrapl. pn'lysis	—	—	—	—	—	—	—	—	—	—	—	—	1	—	0.2	0.2	*1Px 1Ph 1IP 1EP	—	1	—	0.1	0.1	*1Px 1Ph 1IP 1EP	—
Phrenic surgery Extrapl. pn'lysis	—	—	—	—	—	—	8	1	2.9	2.5	1Sc 10Ph 11EP	1Ph 1EP	18	—	3.4	2.7	2Sc 24Ph 21EP	—	26	1	3.0	2.4	3Sc 34Ph 32EP	1Ph 1EP
Extrapl. pn'lysis	—	—	—	—	—	—	3	—	1.0	0.8	3EP	—	3	—	0.6	0.5	5EP	—	6	—	0.7	0.5	8EP	—

Extrapl. pn'lysis	—	—	—	—	—	—	8	1	2.9	2.5	1Sc 10Ph 11EP	1Ph 1EP	18	—	3.4	2.7	2Sc 24Ph 21EP	—	26	1	3.0	2.4	38c 34Ph 32EP	1Ph 1EP
Extrapl. pn'lysis	—	—	—	—	—	—	3	—	1.0	0.8	3EP	—	3	—	0.6	0.5	5EP	—	6	—	0.7	0.5	8EP	—
Pneumothorax Thoracoplasty	—	—	—	—	—	—	—	—	—	—	—	—	5	—	1.0	0.8	5Px 17Th	—	5	—	0.6	0.5	5Px 17Th	—
Pneumothorax Phrenic surgery Thoracoplasty	—	—	—	—	—	—	10	—	3.2	2.7	1Sc *1Px 9Px 12Ph 30Th	—	51	—	9.8	7.8	3Sc 2IN *8Px 43Px 55Ph 159Th	—	61	—	6.9	5.4	4Sc 2IN *9Px 52Px 67Ph 189Th	—
Pneumothorax Intrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	—	—	—	—	—	—	1	—	0.2	0.2	*1Px 2IP 5Th	—	1	—	0.1	0.1	*1Px 2IP 5Th	—
Pneumothorax Phrenic surgery Intrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	—	—	—	—	—	—	4	—	0.8	0.6	4Px 5Ph 5IP 22Th	—	4	—	0.5	0.4	4Px 5Ph 5IP 22Th	—
Pneumothorax Phrenic surgery Extrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	—	—	—	—	—	—	5	—	1.0	0.8	*1Px 4Px 7Ph 7EP 7Th	—	5	—	0.6	0.5	*1Px 4Px 7Ph 7EP 7Th	—
Phrenic surgery Extrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	—	—	—	—	—	—	6	—	1.1	0.9	6Ph 6EP 14Th	—	6	—	0.7	0.5	6Ph 6EP 14Th	—
Phrenic surgery Thoracoplasty	—	—	—	—	—	—	5	—	1.6	1.4	2Sc 1IN 5Ph 16Th	—	18	3	4.0	3.2	2IN 22Ph 63Th	3Ph 6Th	23	3	2.9	2.3	2Sc 3IN 27Ph 79Th	3Ph 6Th
Extrapl. pn'lysis Thoracoplasty	—	—	—	—	—	—	1	—	0.3	0.3	1EP 3Th	—	—	—	—	—	—	—	1	—	0.1	0.1	1EP 3Th	—
Thoracoplasty	—	—	—	—	—	—	4	—	1.3	1.1	9Th	—	2	1	0.6	0.5	7Th	3Th	6	1	0.8	0.6	16Th	3Th
Totals	48	4	100.0	49.5	7Px 70Ph	4Ph	289	24	100.0	85.8	†7Sc †4IN *10Px 131Px 335Ph 16IP 20EP 58Th	†2Sc 4Px 25Ph 1EP	491	30	100.0	79.7	†11Sc †11IN *74Px 293Px 477Ph 72IP 47EP 294Th	*1Px 22Px 16Ph 4IP 9Th	828	58	100.0	78.8	†18Sc †15IN *84Px 431Px 882Ph 88IP 67EP 352Th	†2Sc *1Px 26Px 45Ph 4IP 1EP 9Th

In Columns 5 and 6 of each section, the code letters are interpreted as follows: Px = Pneumothorax, Ph = Phrenic surgery, IP = Intrapleural pneumonolysis, EP = Extrapleural pneumonolysis, Th = Thoracoplasty, Sc = Scalenectomy, IN = Intercostal neurectomy.

* Wherever used in the table indicates bilateral pneumothorax.

† Intercostal neurectomy (IN) and Scalenectomy (Sc) are treated as inserts in Columns 5 and 6 of each section and are not classified at the left of the table, and the number preceding the code letters indicates the number of patients rather than the number of operations.

pneumothorax, of whom 24.1% required nothing more than phrenic surgery. Selections from a group of well developed operative procedures seemed to fit the various treatment indications far better than pneumothorax alone. Exactly 40% of the patients, it will be noted, had these operations either as an adjunct to or in substitution for pneumothorax. Nevertheless, in 70% of the patients in this treatment group of 1124, it was considered either inexpedient or unnecessary to rely on pneumothorax alone, although pneumothorax has been the cardinal standby of comparatively recent years. These statistics provide unquestionable and convincing evidence of the extent to which the third phase of tuberculosis treatment has progressed beyond its initiatory stage.

Unfortunately, lack of space makes it impossible to include in the tables any statistics covering the bilateral or unilateral distribution of these surgical measures. The mass of detail would be too confusing. Some of this information, however, is given under the sections dealing with the individual operations.

Pneumothorax Therapy. In this and the following sections, no attempt is made to estimate the value of the individual collapse procedures in the determination of the final results of treatment. Certain information is of value, however, as indicating the extent of the use of bilateral collapse therapy in the whole program.

In the entire series, bilateral artificial pneumothorax was induced in 85 patients, representing approximately 8% of the whole group, nearly 10% of the surgically treated group, and nearly 16% of all pneumothorax patients. About 20% of those who received nothing but pneumothorax had both lungs collapsed by this method. As indicating the trend for unstable cases with bilateral collapse to accumulate and remain under treatment for much longer than average periods, the percentage of bilateral pneumothorax among all pneumothorax cases was 7.9 for the discharged group, and 28.7 for the resident patients. A reference to Tables 1 and 3 shows that only a negligible percentage of the moderately advanced patients in both groups had bilateral pneumothorax therapy.

Pneumothorax therapy, either unilateral or bilateral, was induced in 542 patients, representing 48.2% of the entire treatment group, and 61.2% of the collapse therapy group of 886 patients (Table 4). In the discharged group of 823, pneumothorax was induced in 3.4% of the minimal, 33.1% of the moderately advanced, and in 53.2% of the far advanced cases, or 41.3% of all discharged patients. Corresponding figures for the classifications of the entire group of 1124 were 6.7%, 39.7% and 59.6%, or 48.2% of the total.

Pneumothorax therapy was later abandoned, for various reasons and at varying intervals, in many of the patients listed above, and in most such instances other surgical procedures were substituted. No attempt is made to classify or explain the limited treatment. No case appears in the statistics, however, in which a partially

effective pneumothorax was not continued for a period of at least one month.

TABLE 4.—USE OF VARIOUS OPERATIONS.

			Discharged patients (823).				Resident patients (301).				Entire group (1124).			
			Cases.	Per cent of 595 surgical.	Per cent of total.	Operations.	Cases.	Per cent of 291 surgical.	Per cent of total.	Operations.	Cases.	Per cent of 886 surgical.	Per cent of total.	Operations.
Pneumothorax	Unilateral		313	52.6	38.0	—	144	49.4	47.8	—	457	51.6	40.6	
	Bilateral		27	4.5	3.2	—	58	19.9	19.2	—	85	9.6	7.6	
Phrenic surgery	Unilateral		493	82.8	59.9	583	229	78.7	76.1	285	722	81.5	64.2	868
	Bilateral		10	1.6	1.2	23	15	5.1	4.9	36	25	2.8	2.2	59
Intrapl. Pnlysis	Closed operation		33	5.5	4.0	35	28	9.6	9.3	30	61	6.8	5.4	65
	Open operation		2	0.3	0.2	2	10	3.4	3.3	11	12	1.4	1.1	13
	Closed and open operations		2	0.3	0.2	4	5	1.7	1.6	10	7	0.8	0.6	14
Extrapl. Pnlysis	Paraffin Plombage	Unilateral	31	5.2	3.7	36	16	5.4	5.3	17	47	5.3	4.2	53
		Bilateral	2	0.3	0.2	4	3	1.0	0.9	6	5	0.6	0.4	10
	Supraperiosteal bag		2	0.3	0.2	3	—	—	—	—	2	0.2	0.2	3
	Supraperiosteal muscle		1	0.2	0.1	1	1	0.3	0.3	1	2	0.2	0.2	2
Thoracoplasty			65	10.9	7.8	187	51	17.5	16.9	174	116	13.1	10.3	361
Multiple intercostal neurectomy			6	1.0	0.7	6	9	3.1	2.9	12	15	1.7	1.3	18
Scalenicctomy			9	1.5	1.0	9	11	3.7	3.6	11	20	2.3	1.8	20
Oleothorax			5	0.8	0.6	—	6	2.0	1.9	—	11	1.2	1.0	

Phrenic Surgery. It has for years been our policy to recommend, with few exceptions, a phrenemphraxis rather than avulsion or section, since we have found that occasionally a permanent paralysis of the diaphragm interferes seriously with later indications for more extensive surgery. Frequently patients have, during their course of treatment, several operations to paralyze temporarily the phrenic nerve for a period of approximately 6 months. Repeated operations inconvenience the patient very little. Occasionally a permanent paralysis is effected before discharge if there is doubt that the patient will take the proper care of himself after discharge, or if the patient is so situated as to make a periodic check of his condition

uncertain. In general, when the patient plans to report several times a year to a good phthisiotherapist, permanent paralysis is postponed indefinitely in all but a few instances. This policy is more rigidly carried out for the younger patients.

No attempt is made in the present study to classify the various indications for phrenic surgery. Its value as a lone procedure is illustrated in Tables 1 to 3, chiefly for the minimal and moderately advanced cases. A total of 747 of the 1124 patients had in all 927 operations, indicating that more than 150 operations were repeated (Table 4). Bilateral paralysis of the diaphragm was effected for 25 patients, who had a total of 59 operations. Very few of this latter group had a simultaneous bilateral paralysis, however. In this bilateral group 2 patients had 4 phrenic operations each, and 5 patients had 3 operations. Of the 722 patients who had unilateral phrenic surgery, 13 minimal, 64 moderately advanced and 52 far advanced cases (129 total) had one or more reoperations. Secondary paralysis was effected in 113 patients, tertiary in 15, and 1 patient had the same nerve paralyzed four times.

Phrenic surgery was used for 66.4% of all the patients treated, and for 84.3% of those surgically treated. As indicated before, it was the only procedure used in 24.1% of all patients, and in 30.6% of the surgically treated patients. Expressed in a more pertinent way, in 36.3% of all the phrenic surgery done no other procedure was added, while 63.7% of phrenic paralyses were performed in conjunction with other collapse measures, either on the same side, or as a lone procedure for the contralateral lung.

Intrapleural Pneumonolysis. The division of pleural adhesions under thoracoscopic control is an extremely valuable procedure in certain instances. The use of this operative procedure to convert and correct an ineffective and at times a dangerous partial pneumothorax collapse will not infrequently avert the necessity for a later thoracoplasty. While it is always advisable to secure the result with a closed operation, the open operation, after partial posterior resection of one rib, or an intercostal incision, is preferable to no attempt at all. The pneumothorax space is infrequently lost after the open operation, and our experience with fluid complications has not impaired our opinion of its value.

Of the 80 patients in this series who had adhesions divided, 7 had both the closed and open operations, and 12 had the open operation alone (usually after inspection had determined the closed operation inadvisable). Of patients with bilateral pneumothorax collapse, 5 had bilateral operations for division of adhesions, in one case both operations being of the open type. A total of 92 operations were performed on the 80 patients. This type of thoracic surgery was used for 9% of the 886 surgically treated patients, and 7.1% of all the patients in the study.

Extrapleural Pneumonolysis with Plombage. While the use of a foreign body to secure a mechanical partial collapse of the lung may not be sound in principle, it has been our experience that such procedure is occasionally justified when all other measures fail to close a cavity, and when there are contraindications to the use of thoracoplasty. In general, an apicolysis with paraffin plombage entails less surgical risk than thoracoplasty. Its indications are limited, however, by anatomic considerations. The results of this operative procedure at this Sanatorium[4] have been such as to justify continued confidence in its importance.

The operation, including 4 supraperiosteal pneumonolyses, was used in this series for 5% of all patients, representing 6.3% of all surgically treated patients. A bilateral paraffin apicolysis was done in 5 cases, and of 47 unilateral operations, paraffin was used both anteriorly and posteriorly in 6 patients, making a total of 63 operations for 52 patients.

The posterior approach in general yields superior results to those secured by an anterior operation. In several patients small bits of paraffin were later expectorated, but no further untoward results were seen in these patients.

Supraperiosteal Pneumonolysis. The indications for this type of extrapleural pneumonolysis are extremely limited. The results secured elsewhere have not been such as to encourage its adoption to any but a strictly limited extent. In our series, 2 patients had an anterior operation with pectoral muscle plombage, and 2 had rubber bag plombage. The latter operation is apparently more effective posteriorly. However, with the use of the bag, periosteal bone regeneration may not occur.

Multiple Intercostal Neurectomy. The indications for this procedure have been limited to patients with unstable unilateral or bilateral disease, for whom other collapse measures have been ineffective, and for whom thoracoplasty is contraindicated at the time. In these cases the results of the operation, either attributed solely to this procedure, or to its effect in preparing the patient for later thoracoplasty, have been so satisfactory that we consider it indispensable in its very limited application. In our series, a total of 15 patients who had this operation represent 1.3% of the entire group, and 1.7% of the surgically treated group. Three cases only had the operation in two stages, and 3 far advanced and 1 moderately advanced case had scaleniectomy as an adjunct. At the present time the operation is being done routinely in two stages.

Scaleniectomy. The results of this operation have not been conclusive enough to justify much confidence in its value as an independent procedure. Our experience with it suggests that its chief value is as an adjunct to multiple intercostal neurectomy, in unstable cases in which the primary object is to secure as much immobility of the hemithorax as possible, in preparation for later

thoracoplasty. Table 4 shows its use in this series in 20 patients, 2.3% of the 886 who had collapse therapy. Table 3 indicates its combination with other operative procedures in 9 moderately advanced and 11 far advanced cases. In 4 cases it was used with multiple intercostal neurectomy, and in 2 cases with phrenic surgery alone.

Thoracoplasty. A total of 361 operations, an average of three stages per patient, were used for the 116 patients for whom this operation was eventually found necessary. At the time of admission, 20 patients had moderately advanced, and 96 far advanced tuberculosis. The incidence of thoracoplasty, therefore, was less than 6% in the 365 moderately advanced cases, and about 15% in 654 far advanced cases, or 10.3% of the entire group of 1124, which includes 105 minimal cases. Thoracoplasty was used for 13.1% of all patients who received any type of collapse therapy. Bilateral partial thoracoplasty was done for one patient only. Thoracoplasty has only rarely been used for moderately advanced tuberculosis, and the majority of the 20 patients mentioned above had considerable progression of the disease before operation.

We believe it to be significant that, in an institution in which the proportion of collapse therapy approximates 80%, and 60% of the cases are far advanced, thoracoplasty should be apparently indicated in only 10% of the patients. The explanation is undoubtedly that, through the judicious selection and use of eight other operative procedures, the necessity for an eventual thoracoplasty in many patients is avoided.

Oleothorax. This procedure, which does not appear in the tables, is of questionable value because of its very limited indications and the uncertain reaction to its use, especially in the presence of positive intrapleural pressures. The occasional acute response of the pleura to its injection and the ever present danger of fistula formation would seem usually to outweigh its possible value in maintaining collapse of the lung in the presence of an obliterative pleuritis, or for certain other indications. In our series, it has been employed in 11 patients, or slightly more than 1% of those who received collapse therapy.

Comment. Recently the development of thoracic surgery (including pneumothorax) was characterized in the literature as an important adjunct to the bed rest regimen. We take some exception to this phraseology. It is more accurate to say that collapse therapy and bed rest are absolutely interdependent upon one another, and that collapse therapy may no longer be considered as a mere adjunct to the more time-honored regimen. We are aware of the approximate fate of patients with pulmonary cavities afforded bed rest alone,[1] and we have statistical proof of the excellent results to be expected following the general use of collapse therapy in large groups of patients.[2,3] There is no question about the indispensable value

of the bed rest regimen for consolidation of the gains effected by collapse therapy. However, those who temporize with bed rest until the need for thoracic surgery becomes urgent are incurring hazards and inviting unfavorable results that far outweigh any of the surgical risks attached to collapse therapy procedures.

It is interesting to note in the literature of recent years that many of those who at one time spoke of "The over-enthusiasm of the exponents of collapse therapy," now exhibit a notable reversal of opinion. Among increasing numbers thoracic surgery is being looked upon more and more as a conservative form of treatment. The more advanced operations, which were formerly considered to be radical surgery, are now accepted as almost entirely routine and unquestionably useful therapy.

With the exception of the following three categories of patients, we believe that practically all patients admitted to a sanatorium with the adult type of active pulmonary tuberculosis, should have collapse therapy: 1, Terminal cases; 2, those whose lesions are only questionably active (the majority of such patients actually do not require hospitalization); 3, those who refuse collapse therapy (the number should be negligible), or who leave the sanatorium for various reasons before collapse therapy is instituted. O'Brien[5] states, "While we all recognize that patients with tuberculosis go through various phases, there is no phase of the disease in which collapse therapy is not indicated except in the terminal one when it is too late."

The paradoxical statement that the so-called radical surgical methods of yesterday have become the conservative treatment of today, applies as accurately to non-cavernous as to cavernous disease. Indeed, in the former group, collapse therapy has a definite prophylactic value in the prevention of cavity formation, and we do not acquiesce in the trite statement that the treatment of tuberculosis is largely the treatment of cavities. There is abundant evidence available that collapse therapy for minimal lesions, and for more extensive lesions without cavity, is productive of much better final results than when similar lesions are not so treated, largely because it tends to forestall the later development of cavities.

There have been many creditable attempts to correlate the expected clinical course of a patient with the pathology of the lesions as interpreted roentgenologically, and to make new classifications of tuberculosis from a prognostic standpoint. We believe that it is still unsafe to translate such classifications from a prognostic to a therapeutic significance. Because of the notorious inaccuracy of prognoses made during the early observation of tuberculous cases, it would seem ill-advised to attempt to classify patients into benign (requiring no collapse therapy) and malignant (requiring collapse therapy) groups. In the present state of our knowledge treatment cannot be predicated upon any of the known prognostic classifica-

tions, if it is to be prescribed within the limits of safety which we must accord the patient as his due. The general use of collapse therapy, with few contraindications, is conservative and should be the accepted procedure.

Summary. 1. Tabulated statistics are presented indicating the extent to which eight collapse therapy procedures, either singly or in various combinations, have been used in a series of 1124 patients.

2. There is an apparent indication that, in sanatoria having facilities available for thoracic surgery, and in which the admission of far advanced, moderately advanced and minimal cases approximates the ratio 6 : 3 : 1, the treatment expectations should be as follows:

(*a*) Artificial pneumothorax as an unaided procedure will suffice for only one-twelfth of all patients; singly or with other procedures it will be used for approximately 50% of all patients, or about 60% of all those surgically treated.

(*b*) Phrenic surgery as an unaided procedure will suffice for approximately one-fourth of all patients admitted; singly or with other procedures it will be used for approximately two-thirds of all patients, or about 85% of all those surgically treated. Phrenic operations will suffice for seven-eighths of the minimal, nearly half the moderately advanced, but only 15% of the far advanced cases.

(*c*) Phrenic surgery in conjunction with pneumothorax will suffice for approximately one-fourth of all patients, or about one-third of those surgically treated.

(*d*) Major thoracic surgery (excluding pneumothorax and phrenic surgery) will be necessary for approximately one-fifth of all the patients admitted, or for more than one-fourth of the collapse therapy group.

(*e*) Thoracoplasty should be required in no more than 10% of all patients, representing about one-eighth of the surgically treated group.

3. Bilateral collapse therapy was used for a total of 160 patients, 14.2% of the entire group, or 18.1% of those who received collapse therapy.

4. The intelligent selection and use of various collapse therapy measures should decrease the necessity for major thoracic surgery, and increase the favorable final results of treatment, in direct proportion to the intensity of such a program in the early stages of treatment.

The authors are indebted to Dr. John Alexander for valuable critical advice in the preparation of this article.

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DEATH FOLLOWING PHRENICECTOMY.

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The lack of unfavorable incidents associated with avulsion of the phrenic nerve in the great majority of cases has caused most surgeons to consider the operation a minor one. This is reflected in the literature by such statements as: "The operation itself is attended with little or no risk to the patient" (Lemon[7]). "Mortality from phrenic exeresis is of course negligible" (O'Brien[9]). "The careful pulling of the nerve out of the chest cavity is not dangerous, as we may say after many hundreds of successful attempts" (Sauerbruch[10]). "Phrenicectomy is a minor operation" (Alexander[1]), and many others. Hedblom[4] recommended it as a test operation in detecting any tendency to respiratory incapacity, especially of the better lung, particularly in patients with low vitality capacity. The fact that the operation is considered such an uneventful one by the medical profession makes a catastrophe particularly embarrassing to explain to the family, who probably have been told about the simple procedure which only takes a few minutes under local anesthesia. Because of this prevailing view we have felt that it was advisable to collect the deaths due to phrenic surgery from the literature and at the same time report 2 additional deaths from our personal experience.

Berry[2] reviewed this subject in an excellent article in 1930. He collected from the literature a series of 4697 cases and found that there were 57 serious complications (1.2%) and 26 (0.55%) fatal cases. This mortality rate is an appreciable one for what is generally considered a minor procedure.

Wirth, Koehn and Jaski[12] reviewed a series of 600 cases listing the following complications: 11 cases of aspiration pneumonia, 6 cases of hemoptysis, 8 cases of dissemination of tuberculosis to the intestinal tract, 5 cases spread to the larynx, 12 cases with acute aggravation of the disease ending in death.

The causes of death in the collected cases are shown in the accompanying chart, a portion of them (14) being taken from Berry's[2] article. A summary of the causes of death shows that by far the largest number of deaths are due to spread and aggravation of the tuberculous disease. We, however, are particularly interested in the group of 8 cases who died a cardiorespiratory death, that is with dyspnea and cyanosis, pulmonary edema and tachycardia. Our 2 cases fall in this group and abstracts from clinical courses follow.

Case Reports. CASE 1.—The patient, a young white female, aged 33, whose past medical history was negative except for an attack of rheumatic fever at 16, was first seen in the outpatient department of the University Hospital on May 10, 1934, with a chief complaint of weakness and loss of weight. In 1932 she had begun to get short of breath while working. This was insidious in onset and was not precipitated by a respiratory infection. She continued to work although the dyspnea was marked and there was some edema of the ankles. A year later, May, 1933, she began to lose weight and felt tired. Rheumatic heart disease was first diagnosed at that time. She was advised to quit work and to stop climbing stairs. In January, 1934, she had a severe attack of bronchitis. With it there was cough and expectoration and the sputum was frequently blood-streaked. The cough and blood-streaked sputum persisted to the time of admission. She had lost 30 pounds in weight in the past year and was finally forced to stop work in March, 1934, because of weakness. Examination at that time showed a poorly nourished white female weighing 97 pounds. There were definite physical signs of tuberculosis in the upper third of the right lung (dullness to percussion, increased vocal resonance and posttussive râles). There was moderate cardiac enlargement and a systolic murmur was heard all over the precordium and transmitted to the axilla. The blood pressure was 110/80. There were no signs of cardiac decompensation. The sputum was repeatedly positive for tubercle bacilli.

Roentgen examination of the chest May 12, 1934, showed: Right lung: infiltration with several moth-eaten cavities in the upper half. Left lung: an increase in the trunk shadows to the apex but no definite infiltration. The heart is enlarged, 64% larger than predicted normal. The costophrenic angles are clear, trachea is in the midline.

This patient had failed to show any improvement on bed rest at home and was admitted to the hospital for some collapse measure. Roentgen examination of the chest on admission showed an increase of the disease in the right lung with more evidence of cavity formation. Pneumothorax was decided upon and 5 treatments were given. Following the second pneumothorax treatment there was an increase in the temperature range up to 102°. Since Roentgen examination of the chest showed only a slight collapse, phrenicectomy was decided upon and done under local anesthesia. The nerve was exposed without difficulty and crushed with a hemostat. She was returned to the ward in good condition, except for some dyspnea. Late in the afternoon of the day of operation she became slightly cyanosed and the pulse was rapid and weak. The cyanosis became worse and the patient was placed in an oxygen tent with only temporary improvement. The dyspnea and cyanosis became more marked, the pulse became weak and thready and the patient died 16 hours after operation. Autopsy permission was not granted. However, the entire clinical picture of the patient postoperatively justifies the conclusion that the death was due directly to cardiac failure. (From the service of Dr. E. L. Eliason.)

CASE 2.—Mrs. J. P., admitted to Service No. 1 Tuberculosis Division, Philadelphia General Hospital, July 7, 1933, complaining of cough, expectoration, loss of weight and weakness for 2 years. Two years prior to admission the patient had been advised to stop work and to rest at home, but was unable to do this because of trying conditions at home. One year prior to admission her sputum was found to be positive for tubercle bacilli and for the past 6 months she has been resting in bed about 16 hours daily. In spite of her attempting to rest at home she grew progressively worse, the cough and sputum increased and she lost 40 pounds in weight. Past medical, family and social history was irrelevant. Physical examination showed: temperature 99.6°, pulse 100, blood pressure 112 systolic, 83 diastolic. In the right lung the percussion note, breath sounds and vocal resonance were appar-

ently normal. A few medium coarse râles were heard on inspiration after cough above the level of the second rib and fourth dorsal spine. In the left lung the percussion note was dull over the front and back, the breath sounds were bronchial and cavernous above the level of the third rib and seventh dorsal spine, with pectoriloquy in this same area and many posttussive râles over front and back. The trachea was displaced to the left. The heart was definitely displaced to the left, but was normal as far as physical examination could determine.

The Roentgen examination of the chest showed: "Right lung: small amount of infiltration in the upper third. Left lung: there is an extremely large cavity filling the entire lung field to the level of the third rib, with some infiltration below." The heart and mediastinum are displaced to the left. The sputum was repeatedly positive for tubercle bacilli.

This patient failed to show any improvement after several months of bed rest. The temperature range continued from 98° to 100°. After 3 months of bed rest there was no progression of disease in the right lung and a phrenic exeresis was decided upon, preliminary to thorocoplasty. On October 31, 1933, left phrenicectomy was done under local anesthesia. The nerve was exposed without difficulty. The nerve was freed, infiltrated with novocaine, sectioned and avulsed, 8 inches being removed. No accessory nerve was seen. The wound was closed in the usual manner and the patient returned to the ward in good condition. The day after operation slight dyspnea and cyanosis were noticed and following this the patient had attacks of dyspnea with increased cyanosis. There was no change in the physical signs in the right lung and there was some improvement in the temperature range. Fluoroscopic examination of the chest showed a rise in the left diaphragm of 5 to 6 cm. The attacks of dyspnea and cyanosis became more marked and more frequent and on the eighth day postoperative the patient died suddenly. Autopsy was performed, with the following findings: "Heart, weight 330 gm.; slightly larger than normal, with left ventricular hypertrophy. The heart cuts with decreased resistance, has a pale pink, cloudy appearance. Valves are grossly negative. Foramen ovale is partially opened. Left lung, weight 48 gm. The upper lobe is almost completely replaced by a cavity the size of a large fist with marked fibrosis. The cavity extends to the pleura and is lined by a thickened, grayish membrane. The lower lobe is compressed. Right lung, weight 530 gm. It pits on pressure and crepitates, except for tiny nodules throughout the upper portion. Upper lobe shows depressed scarred area of old, healed tuberculosis with a cavity 1.5 cm. in diameter underneath the pleura near the apex."

These 2 cases of death following phrenicectomy undoubtedly belong to the group described by some authors as dying from respiratory insufficiency, and by others as due to cardiac failure. The nearest approach to our cases was the case of Weber[11] who advanced the theory that the change of intrathoracic pressure with a shift of the mediastinal structures to the right (right phrenicectomy) was the cause of death in his case. He further brought forth the hypothesis that a left phrenic exeresis might have caused a return to normal relationship and saved the patient's life. In our first case this probably was a factor in addition to the preëxisting mitral lesion. His recommendation of doing a phrenicectomy on the contralateral side seems to be a radical form of therapy and most probably would not give the desired result but would further embarrass the cardiorespiratory system.

The 2 patients presented show evidence of cardiac involvement. The first had a definite mitral murmur and was known to have had rheumatic heart disease for several years prior to surgery. The second at autopsy showed a patent foramen ovale.

Paralysis of the diaphragm on one side frequently displaces the heart and changes its axis. This change increases the work of the heart and may be the precipitating factor in heart failure in cases with some preëxisting damage. Our first patient had an old rheumatic heart disease and in the second this change of position and axis of the heart might have caused the foramen ovale to become patent and in that way precipitate heart failure. These facts would seem to indicate that death was primarily due to a cardiac lesion rather than to a reduction in vital capacity. It must be remembered that reduction in vital capacity can be an important factor. One author states that the vital capacity is decreased as much as 36% by phrenicectomy, while another showed that it was reduced from 500 to 800 cc. In a normal individual the tidal air is only one-seventh of the vital capacity so that one would assume that it would have had to be much reduced pre-operatively for this reduction to have resulted fatally. Unfortunately, no pre-operative vital capacity studies were made in our patients. However in Case 2 there was no subjective dyspnea on moderate activity around the wards. Since these two fatalities, one of us was requested to do a phrenicectomy on a rather ill, advanced tuberculous patient in whom the vital capacity was only 1000 cc. This was thought to be sufficiently low to contraindicate phrenicectomy, as it would decrease the vital capacity to a point dangerously close to the normal tidal air of 500 cc.

The question naturally arises, what can one do to prevent similar catastrophies in the future? The collected mortality rate for this procedure is too high for a so-called simple operation. There is need for more rigid formulation of the indications and contraindications. From our experiences it would appear that any case with evidence of cardiac damage should be carefully observed for some time and a phrenic nerve operation done only after considering the risk and carefully weighing the advantages to be gained. The attitude that the patient is doomed unless something radical is done is not always justified. It may bring into disrepute an operation which is of definite value in properly selected cases. Epstein[3] has proposed the following contraindications: 1. Definite, exudative type of disease. 2. Dissemination of the process in both lungs. 3. Hematogenous forms of tuberculosis. 4. Old cases of fibrocavernous tuberculosis with extensive involvement of the contractility of the lung and secondary heart insufficiency. He speaks of the emphysematous heart and believes that in these chronic cases there is always the danger of right sided heart failure.

Hein[5] suggests close observation of the patient during the period

between injection of local anesthesia and isolation of the nerve with the thought that if untoward symptoms arise (dyspnea, cyanosis and tachycardia) further surgery is contraindicated.

TABLE 1.—RECORDED FATALITIES AFTER PHRENICECTOMY.

Author and reference.	No. of cases.	Cause of death.	Time post-operative.
Berg, W.: Deutsch. med. Wchnschr., **54**, 874, 1928	1	Pulmonary embolism	6 hours.
Chandler, F. G.: Brit. Med. J., **2**, 605, 1928	1	Pulmonary edema	4 hours.
Curti, E.: Policlinico (sez. prat.), **34**, 1474, 1927	1	Dyspnea and tachycardia	10 days.
Dumarest and Berard, L.: Rev. de la tuberc., **9**, 161, 1928	2	Contralateral spread of tuberculosis	?
Deist, H.: Beitr. z. Klin. d. Tuberk., **63**, 424, 1926	2	Pneumonia, pyopneumothorax	?
Hedblom, C. A.: J. Mich. Med. Soc., **28**, 535, 1929	1	Respiratory insufficiency	?
Kleinschmidt, P.: Deutsch. med. Wchnschr., **53**, 473, 1925	2	Hemorrhage caused by avulsion of nerve	?
Morone, G.: Ann. ital. di chir., **4**, 189, 1925	1	Pneumonia	9 days.
Schnippenkotter, W.: Beitr. z. Klin. d. Tuberk., **65**, 56, 1927	1	Spread of tuberculosis	?
Schenck, A.: Ibid., **61**, 552, 1925	1	Contralateral spread of tuberculosis	?
Sergent, E., Baumgartner, R., and Bordet, F.: Bull. et mém. Soc. méd. d. hôp de Paris, **50**, 203, 1926	3	(1) Spontaneous pneumothorax and mediastinal emphysema; (2) on table of asphyxia; (3) hemoptysis 24 hours	1 day.
Zadek, J., quoted by Epstein, D.	5	Pneumonia or spread of tuberculosis	?
Herben, G.: Personal communication to Berry	2	Mediastinal hemorrhage	?
Miller, J. A.: Personal communication to Berry	1	Pneumonia	Several weeks.
Thomopoulos, A., quoted by Berry: Paris, 1925	1	Hemorrhage from pericardiophrenic artery	24 hours.
Berry, F. B.: Arch. Surg., **21**, 1125, 1930	1	Pneumonia and edema	
Cassidy, M. A., and Lee, R. O.: Brit. Med. J., **2**, 684, 1933	1	Asphyxia	On table.
Caralps, M. H.: Assn. Med. Barcelona, **6**, 100, 1930.	1		
Davidson, M., and Ledlie, R. C. B.: Brit. J. Surg., **16**, 198, 1928	1	Pneumonia spread	9 days.
Epstein, D.: Tuberkulose, **12**, 203, 221, 1932	6	Tb. meningitis Dissemination of process Pneumonia Spread of tuberculosis Spread to larynx On table, respiratory insufficiency	6 to 7 days. Not stated. 5 days. About 1 week. Not stated. On table.
Fermandez, G. A.: Med. Ibera, **1**, 496, 1934	1	Hemoptysis	20 days.
Friedrich, S., quoted by Sauerbruch	1	Hemoptysis	Not stated.
Filotta, G.: Riv. san. siciliana, **21**, 438, 1933	1	Hemoptysis	5 days.
Naegli, I.: Zentralbl. f. Chir., **57**, 2962, 1930	1	Hemoptysis	3 days.
Newing, W. J.: Med. J. Australia, **2**, 224, 1934	2 2	Persistent vomiting Hemoptysis	10 days. 14 days.
O'Brien, E. J.: J. Am. Med. Assn., **95**, 650, 652, 1930	1	Pneumonia	Not stated.
Weber, J.: Ibid., **103**, 107, 1934	1	Respiratory failure	6 days.
Zadek, J., and Sonnenfeld, quoted by Epstein, D.	1	Hemoptysis	Not stated.
Cooper, D. A., and Erb, W.	2	Cardiac failure Cardiac failure	16 hours. 7 days.
	48		

Heymer[6,8] suggests temporary paralysis by the injection of novocaine after which the respiratory function is tested by vital-capacity determination and by the length of time the patient can

voluntarily hold his breath (normal 50 to 70 seconds). Of these the first would appear to be too complicated, but the second is of practical value. They state that on the evidence of these tests they have refused to do one phrenicectomy.

TABLE 2.—SUMMARY OF THE CAUSES OF DEATH.

	Cases.
Asphyxia (lung abscess)	1
Cardiorespiratory failure	8
Hemorrhage (surgical)	5
Hemoptysis	7
Pneumonia	7
Pulmonary embolism	1
Pyopneumothorax	1
Pneumothorax and mediastinal emphysema	1
Spread of tuberculous process	13
Vomiting (persistent)	1
Unknown	1
	46

In the Tuberculosis Division of the Philadelphia General Hospital one of us has recommended using a two-stage procedure in any questionable case. In the first instance, the nerve is exposed and injected with novocaine, any accessory nerves are cut and a black silk ligature is drawn around the nerve. The wound is then pulled together by adhesive and the patient observed from a few to 24 hours, when the operation is completed.

Conclusions.—1. Phrenicectomy is not a minor operation, but is attended by an appreciable mortality (0.5%).

2. Forty-four cases of death following phrenicectomy have been collected from the literature, to which 2 additional ones are added.

3. The contraindications to phrenicectomy are discussed. Any cardiac lesion should be considered a contraindication.

4. Pre-operative vital capacity studies should be made routinely.

5. At the time of operation the patient should be observed closely for signs of respiratory or circulatory embarrassment during the induction of the local anesthesia, using also the simple test of the patient's ability to hold his breath.

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CHRONIC MYELOGENOUS LEUKEMIA.

OBSERVATIONS BEFORE AND DURING REMISSIONS INDUCED BY SOLUTION OF POTASSIUM ARSENITE AND BY ROENTGEN THERAPY WITH PARTICULAR REFERENCE TO BONE MARROW.

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THE similarity of the therapeutic response of chronic myelogenous leukemia to Roentgen therapy and to a solution of potassium arsenite has been previously noted.[1] Both result in temporary clinical remission, reduction in the number of total and immature white blood cells, improvement in the anemia and reduction in the elevated basal metabolic rate. A few isolated observations of the bone marrow after treatment suggest that there is a return to red marrow during remissions induced by both Roentgen therapy[2] and solution of potassium arsenite.[3] Reports of detailed studies of the bone marrow before and after treatment have not been encountered in the literature.

This communication presents detailed observations of the peripheral blood, bone marrow, nitrogen balance and oxygen consumption in 2 patients with typical chronic myelogenous leukemia before and during satisfactory remissions induced by solution of potassium arsenite and by Roentgen therapy. The bone marrow findings are of particular interest.

Method. Each patient was admitted to the hospital for a period of observation. Daily white blood cell and differential counts, and frequent estimations of the red blood cells, hemoglobin and reticulocytes were made. The basal metabolism was determined at approximately weekly intervals. A diet of constant protein and caloric content was offered, and record was kept of rejected portions. Daily estimations of urinary nitrogen were made. Nitrogen excreted in the stools was determined in 6-day periods. Biopsy of sternal bone marrow was done in each instance before and after treatment. A small portion of the bone marrow obtained at biopsy was emulsified in serum and studied in supravital preparations and in fixed smears stained with Wright-Giemsa stain. Differential counts of 1000 cells were made in the fixed preparations. The remainder of the bone marrow sample was utilized for paraffin sections prepared in the usual manner and stained with hematoxylin-eosin and eosin-methylene blue.

Case Reports. CASE 1.—E. S., a single Italian girl of 23, had had poliomyelitis at the age of 4 with resultant deformities, including marked scoliosis, atrophy and shortening of the right leg and atrophy of the right arm and hand. She was first seen in this clinic in 1931 because of acute abdominal pain. At laparotomy she was found to have subacute salpingitis. Blood counts at this time were as follows: hemoglobin, 12.8 gm. per 100 cc.; red blood cells, 5,000,000; white blood cells, 11,700 per c.mm.

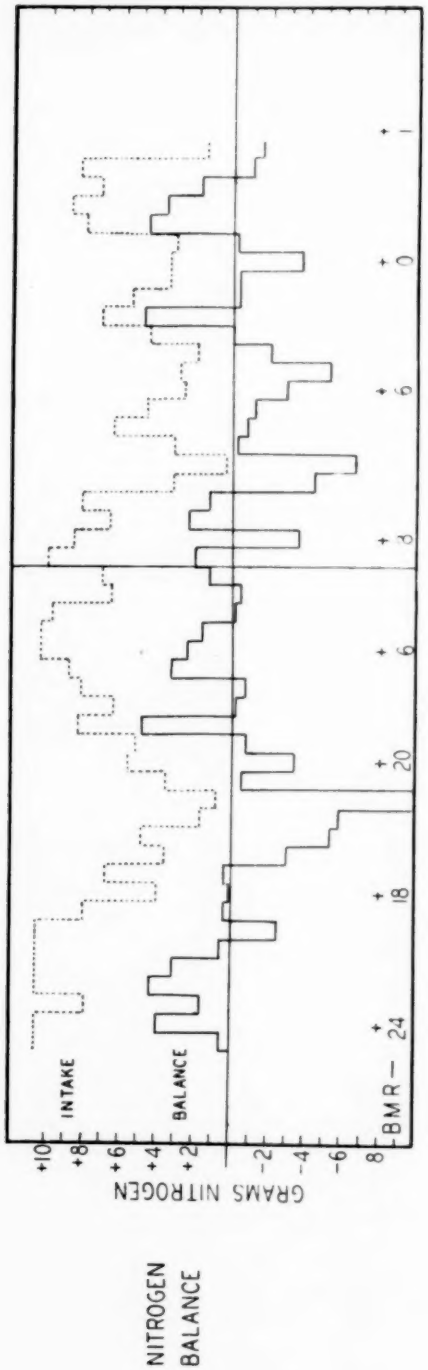

FIG. 1 (*a*)

FIG. 1.—Blood counts, nitrogen balance and oxygen consumption in Case 1.

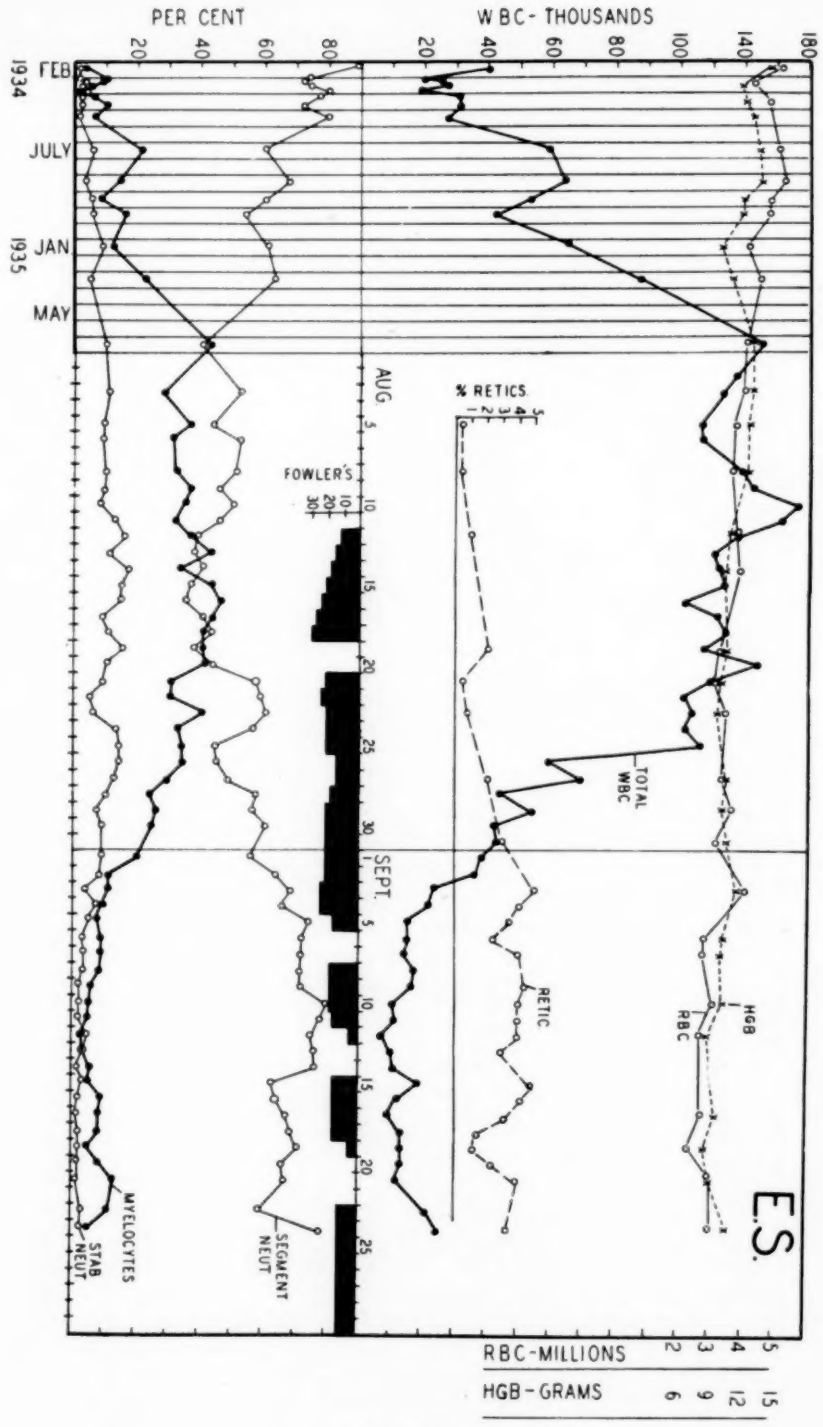
PER CENT
WBC - THOUSANDS
1934 FEB
JULY
1935 JAN
MAY
AUG.
SEPT.
% RETICS
FOWLER'S
TOTAL WBC
RETIC
HGB
RBC
E.S.
MYELOCYTES
STAB NEUT
SEGMENT NEUT
RBC - MILLIONS
HGB - GRAMS

FIG. 1 (*b*).

In August, 1931, she reëntered the hospital with acute arthritis of the left knee and subsequent involvement of other joints, thought to be gonorrheal in nature. Blood hemoglobin was 10.5 gm.; red blood cells, 4,300,000; white blood cells, 15,600 (eosinophils, 2%; basophils, 0.5%; neutrophils, 82.5%; lymphocytes, 12.5%; monocytes, 2.5%). The acute joint symptoms gradually subsided, but arthritic deformities were added to those of the residual poliomyelitis.

In December, 1933, she presented herself with symptoms and signs of secondary syphilis. Dark-field examination of material obtained from ulcerative lesions in the mouth revealed treponema pallida. The Wassermann reaction, which had previously been negative, was 4+. Blood counts were as follows: hemoglobin, 12 gm.; red blood cells, 5,100,000; white blood cells, 13,000, of which 80% were neutrophils. No abnormal cells were found.

The administration of neoarsphenamine was followed by an urticarial reaction. During the following 2 months intramuscular injections of bismuth were given. After receiving a total of 0.8 gm. of "Bismosol," she developed soreness of the mouth and throat, fever, chills and malaise, and again entered the hospital in February, 1934. The significant physical findings at this time, in addition to the skeletal deformities previously noted, included bilateral cervical lymphadenitis and swelling, redness and shallow ulcerative lesions of the tongue, buccal mucous membrane and palate. A marked metallic line was visible at the gum margins. The spleen was not palpable. Material from the ulcers showed many fusiform bacilli and spirillæ. The blood Wassermann reaction was negative. A diagnosis of bismuth stomatitis with superimposed fusospirochetal infection was made. During convalescence from this illness immature granular cells were observed in the peripheral blood for the first time and the presence of early leukemia was suspected. During February and March, 1934, repeated hematologic observations were made. Blood hemoglobin was 14.5 gm.; red blood cells, 5,010,000. White blood cells varied between 19,000 and 40,000 (from 3 to 12% myelocytes, identified repeatedly in both fixed and supravital preparations). For example, on March 5, 1934, the total leukocyte count was 35,600 (basophils, 4.5%; eosinophils, 0.5%; melyocytes, 11%; metamyelocytes, 2%; stab. neutrophils, 3%; segment neutrophils, 71%; lymphocytes, 7.5%; monocytes, 0.5%). Platelets were present in normal numbers. No abnormal red blood cells were found. Supravital (neutral red) differential count was as follows: basophils, 4%; eosinophils, 2%; "C" myelocytes, 11.5%; neutrophils, 75.5%; lymphocytes, 6%; monocytes, 1%. These and subsequent hematologic observations are summarized in Fig. 1. Biopsy of sternal bone marrow was done on March 8, 1934.

During the following 18 months, clinical and hematologic observations were made at intervals. The patient remained clinically well. There was gradual increase in the total white blood cell count and in the percentage of immature cells. On July 30, 1935, the total leukocyte count was 151,000 per c.mm. (basophils, 1%; eosinophils, 3.5%; myelocytes, 30%; metamyelocytes, 13%; stab neutrophils, 41%; lymphocytes, 1.5%. She was without symptoms of any kind. The spleen, however, was felt for the first time, with the edge palpable 5 cm. below the costal margin. There was no lymph gland enlargement. The liver was not palpable. The blood Wassermann reaction was negative, although she had had no antiluetic treatment since January, 1934. On August 2, 1935, the patient was admitted to the hospital for detailed study of the effect of the administration of potassium arsenite.

After a preliminary 10-day period of control observation, Fowler's solution was given in rapidly increasing amounts and continued in sub-

toxic doses. Throughout the period of observation, she continued to feel well, except for recurring symptoms of mild arsenic intoxication. The latter consisted of anorexia, nausea and sometimes vomiting, itching of the eyes, periorbital edema and on one occasion a small area of dermatitis. These symptoms promptly cleared on decreasing or omitting the dose of Fowler's solution for a few days. During her hospital stay, the stools consistently showed occult blood. This was believed to be due to intermittent bleeding of the gums, a symptom which had been present since the bismuth gingivitis in January, 1934. Gastro-intestinal Roentgen-ray studies were negative. Bone marrow biopsy was done on August 8, 1935, before the administration of Fowler's solution was begun, and again on September 12, 1935, at the height of the hematologic remission.

CASE 2.—J. N., a 40-year-old laborer, had the diagnosis of chronic myelogenous leukemia made in 1932. The course of this patient's illness up to August, 1935, has been summarized elsewhere.[3] Treatment between 1932 and January, 1936, had consisted of repeated courses of potassium arsenite and small amounts of Roentgen therapy, of which he had had a total of 2300 Roentgen units.

In January, 1936, he was readmitted to the Strong Memorial Hospital for detailed observation before and after Roentgen therapy. He had had no treatment for the past 3 months, during which time the white blood cell count had been rising. He had been without recent symptoms until 10 days before admission, during which time there had been increasing weakness and fatigue and an uncomfortable feeling of fullness in the left upper quadrant of the abdomen.

The temperature, pulse and respirations were normal. Significant physical findings included moderate pallor, small retinal hemorrhages, hepatomegaly and marked splenomegaly. There was no glandular enlargement.

Red blood cells numbered 3,960,000 per c.mm.; hemoglobin, 10.8 gm. per 100 cc.; white blood cells, 255,000 per c.mm. (basophils, 3%; eosinophils, 1%; myelocytes, 43%; metamyelocytes, 13%; stab neutrophils, 11%; segment neutrophils, 28%; lymphocytes, 1%). Two nucleated red blood cells were found in counting 100 leukocytes. The platelets were abundant. The urine showed a trace of albumin, with rare white blood cells. The blood Wassermann reaction was negative.

After a suitable control period, a total of 1000 Roentgen units were given over the chest and abdomen in divided doses during a period of 7 days. The blood counts, nitrogen balance and determinations of the basal metabolic rate are summarized in Fig. 2. Sternal bone marrow was obtained at biopsy on January 8, 1936, before Roentgen therapy and on February 13, 1936, at the height of the hematologic remission.

Comment. The first patient, E. S., was of particular interest because of the opportunity which was offered to follow the blood picture during the preclinical stage of the disease. It may be noted that the peripheral blood picture led to a suspicion of early myelogenous leukemia, confirmed by bone marrow biopsy, 18 months before the appearance of splenomegaly, which was the first clinical evidence of leukemia. The observations in this patient indicate that the bone marrow changes may precede the leukemic manifestations in the peripheral blood and emphasize the value of bone-marrow biopsy in the early diagnosis of the disease.

The results of treatment are summarized in Figs. 1 and 2. The only clinical changes noted in patient E. S., who was without

symptoms referable to leukemia, was decrease in the size of the spleen during the administration of solution of potassium arsenite. Roentgen therapy was followed by complete, but temporary, disappearance of symptoms in the case of J. N., and by decrease in the size of the spleen.

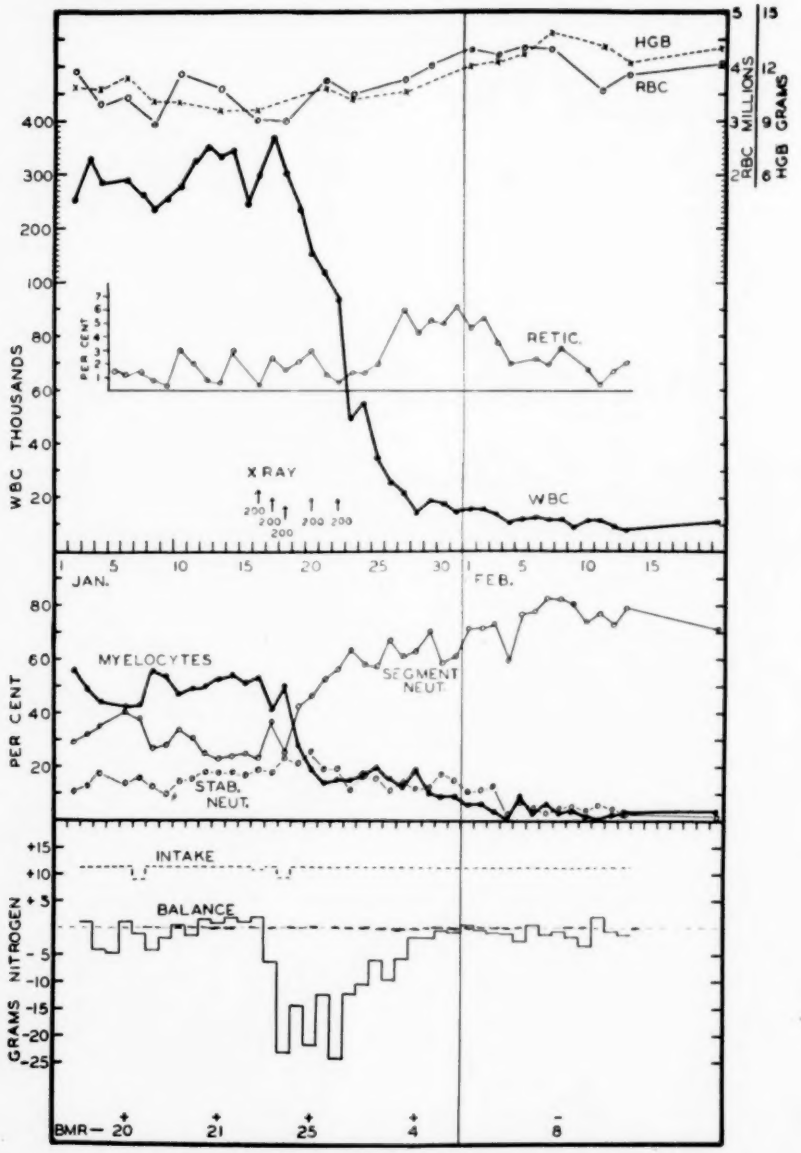

FIG. 2.—Blood counts, nitrogen balance and oxygen consumption in Case 2.

The changes in the blood picture were similar ~~in the 2 cases~~. The administration of both Roentgen therapy and of solution of potassium arsenite was followed by a precipitous decrease in the total leukocyte count to a normal level, a marked increase in the percentage of adult granulocytes and almost complete disappearance of immature cells from the peripheral blood. In each instance, improvement in the white blood-cell picture was followed by a significant increase in reticulocytes and by a subsequent rise in the hemoglobin and the red blood-cell count. No significant change occurred in the platelets.

TABLE 1.—PERIPHERAL BLOOD AND BONE MARROW DIFFERENTIAL COUNTS BEFORE AND AFTER TREATMENT.

	E. S.						J. N.			
	3-8-34.		8-8-35.		9-12-35.		1-8-36.		2-13-36.	
	Blood.	Marrow.	Blood.	Marrow.	Blood.	Marrow.	Blood.	Marrow.	Blood.	Marrow.
Hemoglobin, gm. per 100 cc.	13.2	..	12.3	..	8.7	..	10.2	..	12.3	
R. B. C., millions per c.mm.	4.64	..	3.84	..	2.74	..	2.93	..	3.87	
W. B. C., thousands per c.mm.	26.9	..	139.0	..	7.4	..	237.0	..	8.5	
Reticulocytes, %	..	..	0.4	..	4.0	..	0.8	..	2.0	
	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)	(%)
Basophils	2.0	..	2.5	1.1	2.5	0.6	3.0	0.3	3.5	4.3
Eos. myelocytes	..	1.0	..	1.4	..	0.8	..	1.8	..	0.1
Eosinophils	1.5	1.6	2.0	2.8	2.5	6.1	1.0	3.6	0.5	2.1
Blasts	..	0.6	..	2.8	..	1.6	..	0.3	..	3.2
Myelocytes	9.0	28.4	23.5	33.5	2.0	7.7	46.5	28.2	2.0	14.6
Metamyelocytes	0.5	15.8	8.5	16.2	1.0	4.1	9.0	18.5	0.5	5.0
Stab neutrophils	3.0	20.0	10.0	15.1	4.5	11.7	13.0	24.8	2.5	10.4
Segment neutrophils	74.0	9.6	51.0	14.2	75.5	22.3	27.0	10.2	79.5	15.6
Megaloblasts	..	0.2	..	..	..	1.1	..	0.6	..	0.1
Erythroblasts	..	5.2	..	3.1	..	23.2	..	2.4	..	21.5
Normoblasts	..	3.6	..	2.8	..	8.1	..	1.8	..	6.1
Megakaryocytes	..	..	..	0.1	..	..	..	0.7	..	0.2
Lymphoid cells	10.0	13.2	2.5	3.6	11.5	6.2	0.5	2.0	11.5	11.5
Degenerated cells	..	0.8	..	3.3	..	6.5	..	4.3	..	5.3
Myeloid-erythroid ratio	8.6:1		14.7:1		1.7:1		18.2:1		1.9:1	

The first bone-marrow biopsy in the case of patient E. S. showed changes characteristic of chronic myelogenous leukenia. In the gross, the marrow was gray and appeared very cellular. The bony trabeculæ of the normal sternal marrow had been almost entirely replaced by cellular tissue. The histologic sections showed closely packed masses of immature and adult granulocytes, with scattered erythropoietic elements and only an occasional fat space (Fig. 3). The differential count of the bone-marrow cells (Table 1) showed a marked increase in the myelopoietic elements, with a myeloid-erythroid ratio of 8.6 to 1. The second bone-marrow biopsy, taken 18 months later, but before the institution of therapy, showed more advanced changes, with fat spaces entirely absent and increase in

the myeloid erythroid ratio to 14.7 to 1. The third specimen was obtained at the height of the hematologic remission and showed striking changes. In the gross, the marrow was pale pink in color and there was an abundance of fine bone trabeculæ. The marrow spaces had to a large extent been replaced by rather loose connective tissue. Cellular elements were markedly diminished in comparison with the previous specimens and consisted of islands of myelopoietic and erythropoietic elements scattered throughout the connective-tissue matrix. A marked change was also apparent in the differential count, in that the erythroid-myeloid ratio had returned to an approximately normal value.

Similar changes were noted in the sternal biopsy specimens taken before and after Roentgen therapy in the case of J. N. The first specimen was gray and very cellular, with marked absolute and relative increase in myeloid elements. The second specimen, taken at the height of the remission induced by Roentgen therapy, was pale red in color, with increased bone trabeculæ. Histologic sections showed the marrow spaces occupied by loose connective tissue with marked decrease in the number of hematopoietic cells. Differential counts showed a decrease in the myeloid-erythroid ratio from 18.2 to 1 before treatment to 1.9 to 1 after therapy.

The observed bone-marrow changes were striking and were similar in character and extent in the 2 patients. It is of interest that remissions induced by Roentgen therapy and by solution of potassium arsenite were characterized by similar changes in the bone marrow, as well as in the clinical picture, the peripheral blood and the basal metabolic rate. It should be noted that, although the differential count of the bone marrow approached normal during the therapeutically induced remissions, the histologic picture was quite different from that of normal bone marrow. Fat spaces were not apparent and the number of cellular elements present in a given area was much less than one sees in normal sternal marrow. The changes observed during remission were apparently reversible, for patient J. N. had experienced similar remissions induced by previous courses of both Roentgen therapy and solution of potassium arsenite. Within a few months after the observations here recorded, both patients experienced clinical and hematologic relapses requiring further treatment. It would have been of interest to follow the bone marrow through subsequent relapses and remissions but we did not feel justified in requesting the patients to submit to further biopsies.

We have considered the possibility that the therapy may not have been responsible for the bone-marrow changes observed during the remissions. It is possible, that, on these occasions, a non-representative area of relatively hypoplastic marrow may have been encountered; such areas, however, are much less likely to occur in the sternum than in the long bones. Another possibility to be con-

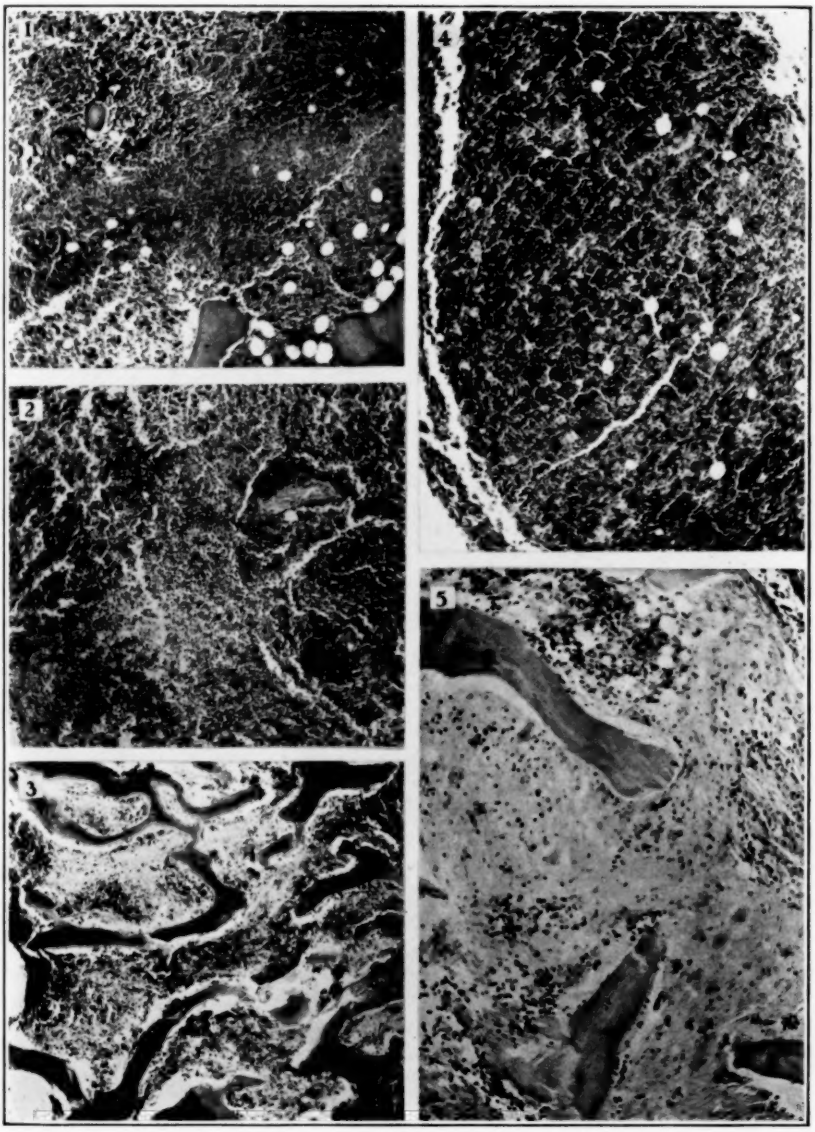

FIG. 3.—Photomicrographs of sternal bone marrow before and after treatment. (1) E. S., 3-8-34 (× 100); (2) E. S., 8-8-35 (× 100); (3) E. S., 9-12-35 (× 100); (4) J. N., 1-8-36 (× 150); (5) J. N., 2-13-36 (× 150).

sidered, particularly in view of the connective-tissue reaction in the marrow cavity, is that the changes observed in the last biopsy in each instance, may have been due to tissue reaction resulting from the mechanical interference of the previous biopsy. This is considered unlikely, inasmuch as the later biopsies were made a distance of at least 3 cm. from the previous operative site. The changes observed in the bone marrow of these 2 patients, particularly as regards the differential counts, were compatible with the coincident changes in the peripheral blood, and were interpreted as being due to the therapeutic influence of the solution of potassium arsenite and the Roentgen therapy, respectively. Observations made in a larger number of cases will be necessary before it may be concluded that such changes are characteristic of therapeutically induced remissions in myelogenous leukemia.

The basal metabolic rate determinations showed changes similar to those reported elsewhere[2] and require little comment. Before treatment both patients exhibited a moderate increase in oxygen consumption, which fell to a normal level during remission.

The nitrogen balances are of interest because they constitute the only essential respect in which the response to the two therapeutic agents differed. Patient E. S., who received solution of potassium arsenite, showed no significant change in the nitrogen balance, although a marked decrease in the white blood-cell count was observed. On several occasions the nitrogen output exceeded the nitrogen intake. However, the periods of negative nitrogen balance, which was never of great magnitude, were of short duration and occurred at a time when the nitrogen intake was curtailed because of gastro-intestinal reaction to the large doses of Fowler's solution. Furthermore, during the period of rapid fall in the white blood-cell count, the excretion of nitrogen was slightly less than the intake. During the entire period of observation the nitrogen excretion exceeded the nitrogen intake by only 14.1 gm., a figure considered to be within the range of technical error. The weight decreased from 43 to 40.2 kg., the non-protein nitrogen of the blood was reduced from 38 mg.% at the beginning of the experiment to 26 at the conclusion of the period of observation. It may be concluded that, in this particular instance, the induction of a remission by the use of solution of potassium arsenite resulted in no significant change in the nitrogen balance.

It is well known that the use of Roentgen therapy in leukemia ordinarily is followed by an increase in the nitrogen excretion. This is usually interpreted as the result of the destruction of large numbers of white blood cells. Patient J. N. exhibited a marked negative balance during and after Roentgen therapy. During the period of observation, nitrogen excretion exceeded the nitrogen intake by 171.5 gm., the weight decreased from 74 to 70 kg., the non-

protein nitrogen of the blood dropped from 45 to 29 mg.%. Although the negative nitrogen balance persisted during the fall in the white blood cell count, it should be noted that the peak of nitrogen excretion occurred 2 days before there was any significant change in the leukocyte count. These observations, together with the fact that the irradiation of normal animals and of patients with malignant disease results in increased nitrogen elimination,[4] suggests that the negative nitrogen balance observed after Roentgen therapy in leukemia is related primarily to effects other than those on the circulating leukocytes. Further observations will be necessary before definite conclusions may be ventured in this regard.

No attempt has been made to draw sweeping or generalized conclusions as to the effect of solution of potassium arsenite or Roentgen therapy on the bone marrow and nitrogen metabolism in this disease. Rather, the data are reported as detailed observations in two typical instances of chronic myelogenous leukemia, with characteristic remissions following treatment with these two agents. It is recognized that there are wide variations in both the clinical and hematologic picture of the disease and in the response to both forms of therapy. The question as to whether the observations made in these patients, particularly in regard to the changes in the bone marrow, represent the typical response in therapeutically induced remissions of the disease, must be decided by further investigation.

Summary. 1. Detailed observations of the peripheral blood, bone marrow oxygen consumption and nitrogen balance were made in 2 patients with typical chronic myelogenous leukemia before and during characteristic remissions induced by solution of potassium arsenite and Roentgen therapy.

2. In each instance, treatment was followed by (*a*) clinical improvement, (*b*) reduction of the total leukocyte count to a normal level, (*c*) marked decrease in immature cells, (*d*) reticulocytosis, (*e*) improvement in the anemia, (*f*) return of the oxygen consumption to a normal level, (*g*) striking changes in the bone marrow.

3. In each instance the gray, hyperplastic, cellular leukemic bone marrow was replaced (presumably temporarily) by a relatively hypocellular, fibrotic marrow and the markedly increased myeloid-erythroid ratio was decreased to an approximately normal level.

4. Roentgen therapy was followed by a marked increase in the nitrogen excretion. The administration of solution of potassium arsenite was followed by no significant change in the nitrogen balance.

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THE EFFECT OF THE SUBCUTANEOUS INJECTION OF ADRENALIN ON THE LEUKOCYTE COUNT OF SPLENECTOMIZED PATIENTS AND OF PATIENTS WITH CERTAIN DISEASES OF THE HEMATOPOIETIC AND LYMPHATIC SYSTEMS.*

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It is a well-known fact that the subcutaneous injection of adrenalin produces a leukocytosis in the peripheral blood. The mechanism of this action is still not definitely understood.

Oliver and Schäfer[26] found that an extract prepared from the suprarenal glands was capable of producing contraction of the spleen when injected into laboratory animals. Schäfer and Moore[30] showed that this extract produced a similar effect on the excised spleen of laboratory animals. Loeper and Crouzon[20] noted that, in both rabbits and man, the injection of adrenalin produced a slight but variable *decrease* in the red blood cell count, as well as an increase in the white blood cell count. They found also that the increase in the number of lymphocytes occurred earlier, and disappeared sooner, than that of the neutrophils.

Frey and his co-workers[13–15] and also Hatiegan[17] showed that in normal individuals a leukocytic response of distinctive character followed the injection of adrenalin. This response occurred in 2 phases: the first phase was noted soon after injection, and consisted of a sharp increase in the absolute and relative numbers of lymphocytes; the second followed at the end of an hour and consisted of a decrease in the number of lymphocytes and an increase in the neutrophils. Frey was unable to demonstrate this characteristic reaction in patients who had undergone splenectomy, or in those in whom the architecture of the spleen had been grossly altered by disease, such as, for example, in advanced Banti's syndrome. From these experiments he concluded: 1, that adrenalin induced leukocytosis by causing contraction of the spleen and the expression of blood cells into the general circulation; 2, that, since the lymphocytic response does not occur following removal of the spleen or when disease has caused widespread alteration in the structure of the organ, the test is of value in determining splenic function.

* Assisted by a grant from the Christine Breon Fund.

Barcroft[2-4] showed that the spleen contracts following a number of altered physiologic conditions, including hemorrhage, asphyxia, exercise, and changes caused by psychic disturbances. From his observations he concluded that the spleen acts as a reservoir for blood cells which controls, to a certain extent, the volume of the circulating blood.

Investigations made since the studies of Frey have been the basis for diverse opinions. There is general agreement that injection of adrenalin produces leukocytosis, and that an increase in lymphocytes precedes that of neutrophils.

Attempts to explain the mechanism of leukocytosis following the injection of adrenalin have prompted the following hypotheses:

1. *Splenic Contraction.* Since the early work of Frey, it has been assumed that splenic contraction plays an important part in the production of the leukocytosis.[13-15,2-5,8,11,21,24,25,31,34,35,37,38] Numerous experiments and observations, however, have shown that contraction of the spleen is not necessary for the production of the leukocytosis, and that the leukocytosis may occur after the spleen has been removed.[7,9,18,22,27-29,33,36]

2. *Hemoconcentration.* According to this hypothesis, the volume of the circulating formed elements of the blood can be increased relatively by a loss of plasma fluids into the tissues.[31] It has been demonstrated that adrenalin obstructs the venous outflow from the liver, increases the portal pressure, and favors the passage of fluid into the lymphatics of the liver, resulting in a concentration of the cellular elements of the circulating blood.[10,16,19,23] Yang and Chang[38] could find no significant changes in the volume of the blood following the use of adrenalin.

3. *Direct Stimulation of the Bone Marrow.* Walterhöfer[35] demonstrated changes in the bone marrow of rabbits following repeated injections of adrenalin. Auricchio[1] and Edmunds and Stone[12] considered the leukocytosis as *probably* due to direct stimulation of the bone marrow.

4. *Redistribution of Formed Elements of the Blood.* Because of the vasoconstrictor and pressor effects of adrenalin, it has been held that cells which are lying immobile and in contact, centrally and peripherally, with the walls of the blood vessels are forced into the axial stream when this drug is injected.[25] It has been stated, therefore, that the leukocytosis is due entirely to peripheral vascular and capillary constriction.[12,29]

5. *Expulsion of Leukocytes from Lymph Nodes.* Many authors,[7,11,12,31,35] have regarded direct stimulation of the lymph nodes as a cause of the leukocytosis. Martin[22] has shown that lymph nodes can be made to contract when stimulated with adrenalin. Since it is impossible to exclude the lymphoid tissue from the circulation, experimental proof of the part played by the lymph nodes is lacking.

The leukocytosis has also been attributed to stimulation of the vegetative nervous system;[6] and likewise to the synergistic effect of alterations in the hydrogen-ion concentration within the hematopoietic organs and locally in the smaller blood vessels.[9, 21]

In an attempt to determine whether the leukocytosis is due to direct stimulation of the hematopoietic organs or to an indirect action upon the peripheral vascular system, the effects of adrenalin stimulation on the leukocyte counts of 33 patients were studied. Seven patients who had undergone splenectomy were studied, for observation of the effect of removal of the spleen upon the results of the test. Four of these were tested before, as well as following, splenectomy. In addition, there were studied 7 patients diagnosed as having Hodgkin's disease; 7 with anemia and splenomegaly; 4 with luetic hepatosplenomegaly; 4 with tuberculous adenitis; and 4 with myeloid leukemia.

Methods. Each patient was injected with a single dose of 1 cc. of a 1 to 1000 solution of adrenalin hydrochloride (Parke-Davis), administered subcutaneously in the deltoid region. Blood pressure readings were taken shortly before, and 10 minutes after, injection. Most of the patients experienced the usual and characteristic reactions of anxiety, palpitation, hyperidrosis, tremor and elevated blood pressure. Some patients complained of *soreness in the region of the spleen, and tenderness over the long bones.*

All blood counts were made using certified (U. S. Bureau of Standards) pipettes and hemocytometers. Differential blood counts were made on cover-slip preparations stained by the Jenner-Giemsa method. Complete studies of the capillary blood, including hemoglobin determination, erythrocyte, leukocyte, differential and platelet counts, were made before inoculation. Leukocyte and differential counts were made at intervals of 10, 20, 40, 60 and 100 minutes after inoculation.

In as many instances as possible the diagnoses were verified by pathologic examination of tissue removed by biopsy, and in 1 case by autopsy.

Results. The results are shown graphically in the accompanying figure (Chart I). The values are expressed as averages in terms of absolute numbers of each cell type per cc. of blood. A description of the results in the patients studied following splenectomy, and those of the various diagnostic groups in our series, are given below:

1. *Following Splenectomy.* In the 7 patients who were tested following removal of the spleen, there was a slight leukocytosis (average 11,400) before the injection of adrenalin. Following the injection there was a rapid increase in number of leukocytes, so that at 10 minutes the total count was slightly more than doubled. The marked leukocytosis persisted to the end of an hour. At 100 minutes the total count had dropped, but was still considerably higher (average 18,000) than before the injection. The early rapid increase in the number of leukocytes was characterized by a marked lymphocytosis, an unusual feature of these cases. The neutrophils and monocytes also showed a considerable increase. At the end of 40 minutes the

lymphocytes and monocytes had decreased, but the neutrophils were still rising, reaching a maximum at the 60-minute count. The

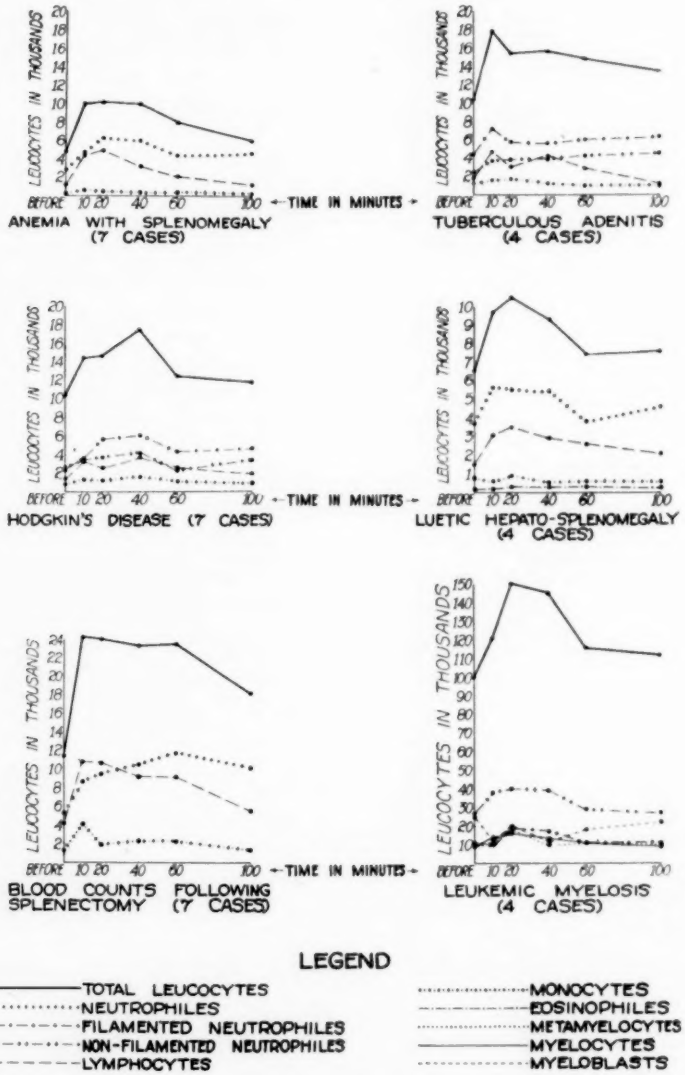

CHART 1.—Average blood counts before and after the subcutaneous injection of adrenalin (1 cc. 1 to 1,000.)

sustained neutrophilia was responsible for the persistent leukocytosis. With the exception of the case of erythroblastic anemia recorded below, no immature cells were observed at any time.

Adrenalin tests were performed on 4 of these patients before, as well as following, splenectomy. In the tests performed before operation, the curve in no instance resembled that following splenectomy. It would appear, from these studies, that the subcutaneous injection of adrenalin in the splenectomized person produces a marked, persistent leukocytosis of normal blood cells characterized by a conspicuous lymphocytosis followed by a neutrophilia which persisted throughout the test.

In the following table are recorded the results of an adrenalin test done on a young boy of Greek parentage who had had his spleen removed 2 years previously and on whom the diagnosis of erythroblastic anemia had been established.

ADRENALIN TEST.

August 6, 1935.
S. P., male, aged 12. Parentage, Greek.
Diagnosis: Erythroblastic anemia; spleen removed, 1933.
Injection: 1 cc. 1/1000 adrenalin hydrochloride, subcutaneously.

	Before.	10 min.	20 min.	40 min.	60 min.	100 min. after.
Hemoglobin	40% (5.6gm.)					
Red blood cells (millions)	3 12					
Platelets	500,000	Greatly incr.				
Nucleated red blood cells	77,100	84,100	98,700	105,700	90,600	74,000
White blood cells corrected	18,100	79,500	67,700	46,300	50,600	32,000
Neutrophils: Filamented	6,154	11,925	18,956	12,038	14,168	11,200
Non-filamented	543	795	677	....	...	320
Eosinophils	1,086	3,975	2,708	2,315	1,012	320
Basophils	362	...	...	....	506	320
Large lymphocytes	....	...	...	....	1,012	320
Small lymphocytes	7,602	47,700	38,589	22,687	25,806	14,080
Monocytes	1,991	12,720	3,385	6,482	6,578	4,800
Metamyelocytes	....	...	...	463		
Myelocytes	181	795	....	463	1,012	640
Blasts	....	...	2,031	926		
Unclassified	181	1,590	1,354	926	506	

In this case the leukocyte response is similar in type to that found in the group discussed above. The nucleated red blood corpuscle count reaches its highest level at 40 minutes and returns to the pre-injection level at 100 minutes. The maximum neutrophil count appears at 20 minutes, and the lymphocytes and monocytes reach their maximum in 10 minutes. At 100 minutes the levels of the latter three types of cells remain elevated in direct proportion to the degree of leukocytosis. When the immature types of leukocytes are studied as a group, one notes that at 20 and 40 minutes they are apparently increased out of proportion to the total leukocyte count.

2. *Anemia With Splenomegaly* (7 Cases). This diagnostic term is used in preference to the controversial one of "Banti's syndrome," although 4 of the 7 patients exhibited the disease-course which is usually regarded as typical of Banti's syndrome. Before injection a leukopenia was found in all patients. Following injection, there was a sharp rise in the total leukocyte count, so that at the end of 10 minutes the number of white blood cells had doubled. Within 60 minutes the total leukocyte count had fallen, and at the end of 100 minutes it showed a gradual trend toward the original level. The lymphocytes showed an early sharp rise followed by an early fall, so that within 100 minutes they had returned to the original level. The neutrophils increased more slowly, but the rise was sustained longer, and a slight secondary rise was noted between 60 and 100 minutes. The other cellular elements were not markedly affected.

3. *Tuberculous Adenitis* (4 Cases). Before administration of adrenalin, there was a slight elevation of the leukocyte count. Following the injection, there was a sharp increase in the total average count (from 10,500 to 18,000 in 10 minutes). By the end of 20 minutes there was a slight decrease and then a fairly well-sustained high level to 100 minutes. The increase in number of lymphocytes and of neutrophils occurred simultaneously with a relatively greater increase in the lymphocytes. Within 100 minutes, the lymphocytes had decreased in number to a point below the original level while the neutrophils showed a secondary increase between 40 and 100 minutes, and at 100 minutes had reached a level of 50% greater than before the injection. Contrary to the reports of other authors,[32, 36] we did not find a significant increase of monocytes. One patient with tuberculous cervical lymphadenitis complained of soreness and pain in the region of the affected lymph nodes after the injection of adrenalin.

4. *Hodgkin's Disease* (7 Cases). Before injection, there was a slight leukocytosis, with both absolute and relative neutrophilia. Within 10 minutes after the injection, there was a sharp increase in the total average leukocyte count (from 10,400 to 14,500). The highest count (average 17,500) was observed at 40 minutes. The neutrophils showed the greatest relative increase with a secondary rise, particularly of the non-filamented forms, between 60 and 100 minutes. The lymphocytes showed a secondary rise between 20 and 40 minutes, followed by a gradual return toward the normal level. In general, the curve of the monocytes paralleled that of the lymphocytes. In 1 case, a few primitive monocytes were seen. Three patients complained of pain in the region of the spleen, one of whom complained also of pain over the long bones. Autopsy of the patient last mentioned showed the bone marrow infiltrated with cells characteristic of Hodgkin's disease.

5. *Luetic Hepatosplenomegaly* (4 Cases). Before injection, the leukocyte counts were within normal limits. Within 10 minutes after the injection, a definite leukocytosis had occurred, the highest total counts being recorded at 20 minutes. The increase in number of lymphocytes was relatively greater than that of the neutrophils; however, the neutrophilia was sustained longer. The lymphocytosis at the 20-minute count was a conspicuous feature of these cases. After the first sharp increase, the lymphocytes showed a gradual decrease toward their original number. At 60 minutes, the neutrophil count had returned to the level found before injection. A secondary rise in the neutrophils was observed at 100 minutes. No immature cells were seen.

6. *Leukemic Myelosis* (4 Cases). The average total leukocyte count before the injection of adrenalin was 100,000. Following the injection there was a rapid rise to 150,000 white blood cells at 20 minutes. At 60 minutes the count was 112,000. The non-filamented neutrophils rose from an average of 27,000 before the injection to 40,000, 20 minutes after, and then showed a gradual return to the original level. The number of filamented neutrophils decreased slightly during the first 10-minute interval, then rose sharply at the 20-minute interval and gradually returned to the original level. The myelocytes increased from 9000 to 16,000 at 20 minutes and returned to 9000 at 100 minutes. The metamyelocytes followed a similar course. The myeloblasts were decreased in number following the injection, and then rose gradually to reach their original level within 100 minutes. From these studies one cannot say that the abnormal forms were specifically stimulated by the injection of adrenalin. All patients complained of pain in the region of the spleen. One patient complained of aching pain over the long bones, as well as pain over the ribs and sternum.

Discussion. While it was not our intention in this study to explain the mechanism of the leukocytic response to adrenalin, we believe that our results help to throw some light on this phenomenon. Most noteworthy is the fact that the blood of patients whose spleens had been removed exhibited a response which, in its general features, was not very different from that found by other investigators. This would indicate that, while the spleen may contract and discharge a relatively large volume of blood into the circulation, it cannot be the only causative factor in the phenomenon of leukocytosis following the injection of adrenalin.

Worthy of consideration also is the finding of very few immature cells in the peripheral blood. If it were true that the increase in white blood cells is due to the sudden expression of cells from the bone marrow into the general circulation, one would expect to find, especially in the myeloid leukemias, a fairly large proportion of immature cell forms. That such was not the case, is an argument against the hypothesis that stimulation of the bone marrow plays

an important rôle in the leukocytosis. A more probable explanation is that the increase in number of leukocytes is chiefly due to the redistribution of formed elements of the blood, or altered relationships between the volume of blood cells and plasma.

In each disease group studied, a somewhat different response was obtained. However, certain features were consistently noted. In all instances, there was a definite increase in the number of leukocytes following the subcutaneous injection of adrenalin. With few exceptions, the leukocytosis consisted entirely of an increase in the number of normal lymphocytic and granular cell elements. In general, except in the cases of myeloid leukemia, the lymphocytes showed an earlier and more rapid, as well as relatively greater, increase. The granular cells showed a later but longer-sustained increase, with a tendency toward a secondary rise.

Summary. 1. In all patients studied, the injection of adrenalin was followed by a definite leukocytosis.

a, The blood of patients who had undergone splenectomy showed a leukocytic response differing little from that of patients whose spleens had not been removed.

b, The lymphocytes showed an earlier and relatively greater increase than that of the other cellular elements.

c, With the exception of a case of erythroblastic anemia, immature cell forms did not appear in the circulation in numbers sufficient to warrant the conclusion that the bone marrow was stimulated.

2. The results of the adrenalin test in a patient who was diagnosed as having erythroblastic anemia and whose spleen had been removed is recorded.

3. As a result of these studies, no definite diagnostic value can be attributed to the leukocytosis which follows the subcutaneous injection of adrenalin.

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PAROXYSMAL COMPLETE HEART BLOCK ALTERNATING WITH NORMAL RHYTHM AND CONDUCTION.

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Complete auriculoventricular heart block alternating with normal rhythm and conduction is regarded as an unusually rare occurrence. Its rarity can be judged by the fact that complete heart block itself is an uncommon disorder, only being found in approximately 0.55% of cases with known or suspected cardiovascular disease.[6,12] It is the purpose of this study to review critically the reported cases of this type of paroxysmal complete heart block and to present a new one. The present case first showed periods of complete heart block with Adams-Stokes' syndrome which alternated with periods of normal conduction and later developed a chronic complete block with the coincident disappearance of the syncopal attacks.

Review of Literature. *Criteria.* It is obvious that graphic records are necessary to establish proof that paroxysmal *A-V* block exists (White).[30] Consequently only those reports which had either polygraphic or electrocardiographic records were studied, and in these the graphic tracings were examined in detail. Only those cases were selected in which there was clear evidence that normal conduction and complete heart block with an idioventricular rhythm existed independently and periodically. The occurrence at times of an additional partial block, a frequent finding in these

cases, was not an eliminating factor. A *P-R* interval of 0.20 second or less was regarded as normal. Cases in which the block was in the nature of a ventricular standstill without a subsequent idioventricular rhythm were not included. It was felt that such cases did not belong in a group in which an independent ventricular rhythm was definitely established.

Summary of Cases. Twenty cases previously included or potentially falling into this group were found in the literature. Of these, only 12 met with the established criteria. The remaining 8 have been excluded for reasons to be given herewith. Gibson and Ritchie,[11] and Gager[7] each reported a potential case. The former was excluded because of insufficient graphic evidence, the latter because the *P-R* interval during normal rhythm was slightly prolonged (0.24 second). Gossage's[13] case was eliminated because there was no clear evidence that complete *A-V* dissociation existed. The cases of Starling[27] and Lewis[17a] showed ventricular standstill with no definite idioventricular rhythm. No graphic evidence was presented in Case 1 of Mackintosh and Falconer[19] to establish the transient nature of the complete heart block which developed the day after admission and persisted. In Case 2 of the same authors, however, there was sufficient evidence to warrant its inclusion in this series. The case report by Cohn, Holmes, and Lewis[5] contained two tracings, both of which showed only a high degree of partial block. In a case reported by Wilson and Robinson[31] normal conduction was not established until long after the complete heart block had disappeared.

The more important data of the acceptable 12 cases and of the present case have been tabulated for convenience in Table 1. This table needs no further explanation other than to mention that some of the data have been estimated from the published tracings when such data were not specifically mentioned in the text.

Pathology. The heart was examined after death in only 4 cases of this series. In the case of Gager and Pardee[8] a calcified ring was found around the left auriculoventricular orifice. The bundle of His was grossly normal but there was no histologic examination and consequently little of definite value is contributed by this report. Russell-Wells and Wiltshire[24] found a heart with calcified aortic cusps and a fibrocalcareous mass in the left upper ventricular septum. Histologically, the *A-V* node and the bundle of His were in immediate contact with this mass. The tissue of the node and bundle showed the effects of chronic inflammation and, in addition, there was an area showing the presence of subacute inflammation. The coronary vessels were not particularly sclerotic. These authors concluded that the encroachment of the mass plus fluctuating degrees of inflammation on the basis of an infectious endocarditis, type not determined, had been responsible for the clinical findings. In the case reported by Yater and Willius,[34]

Fig. 1

Fig. 2

Fig. 3

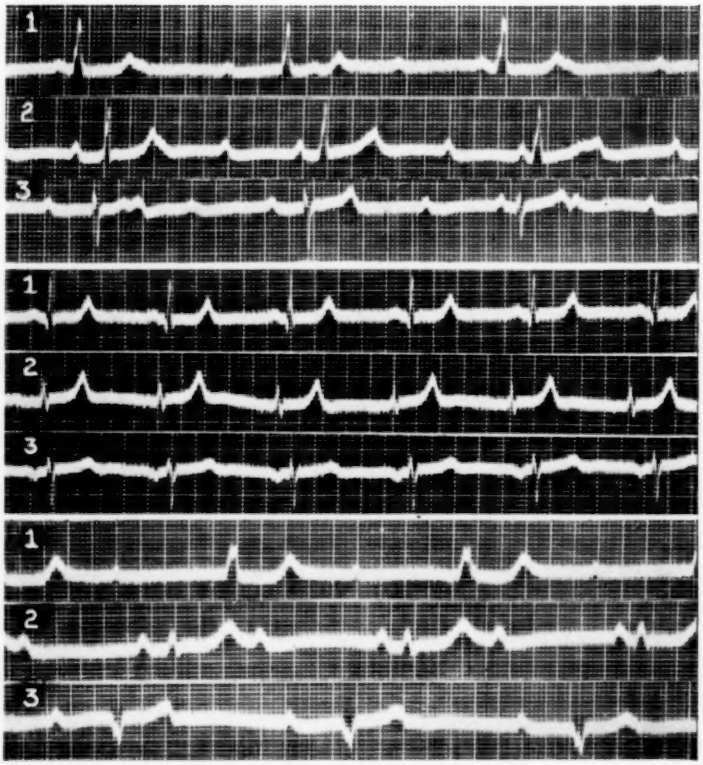

Fig. 1.—Transient complete heart block.
Fig. 2.—Normal rhythm. *P-R* interval 0.18 second
Fig. 3.—Chronic complete heart block.

Table 1.—Cases of Paroxysmal Complete Heart Block.

Graphic tracings.

TABLE I.—CASES OF PAROXYSMAL COMPLETE HEART BLOCK.

Cases.	Age at onset.	Sex.	Duration.	Etiology.	Graphic tracings. Ecg or polygram.	Normal. Rate per min.	Normal. P-R or A-C	Normal. QRS.	Complete heart block. Rate per min. A	Complete heart block. Rate per min. V	Complete heart block. QRS.	Additional partial block.	Other findings.	Notes.	Outcome with time after onset.
1. Thayer and Peabody; Earnshaw[28] (Case 1)	53 yrs.	M	5 mos.	? Arteriosclerosis	P	70 to 80	.18 to .20	..	120 to 130	30	.. ..	High degree	.....	Atrop. grs. 1/60 abolished part. block. Atrop. grs. 1/30 had no effect on comp. block.	Well.
2. Mackintosh and Falconer[19] (Case2)	71	M	3	Arteriosclerosis	P	..	.20					High degree	Nor. conduction foll. by vent. standstill. Then an idiovent. rhythm. Then part. block.	Atrop. grs. 1/100 t.i.d. gave relief from A-S attacks	Died in convulsions (3½ yrs.).
3. Simon and Robinson[26]	65 yrs.	M	3½ yrs.	Arteriosclerosis*	ECG	56 to 84	.19 to .20	.145 to .159	84	20	.192	.....	Right bundle-branch block in comp. block (Fig. 2)*	Atrop. grs. 1/50, exercise, and vagal pressure had on effect on comp. block on	Died (3½ yrs.).
4. Russell-Wells and Wiltshire[24]	44 yrs.	M	12 yrs.	Infectious endocarditis	ECG	62 to 82	.20	Normal*	75*	49 to 51	Normal*		Aur. fibrillation in comp. block (final state)	.....	Died of ca. of cecum (12 yrs.)
5. Carter and Dieuaide[2]	67 yrs.	M	3½ yrs.	Arteriosclerosis*	ECG	78	.17	.12	78	16 to 30	.15		Partial rt. bundle-branch block with both nor. rhythm and comp. block	Atrop. 2 mgm. had no effect on block. Vagal pressure decr. rate from 67 to 52 and incr. P-R from .18 to .20.	Died . Last 4 mos. no attacks (3½ yrs.).
6. Gager and Pardee[8]	59 yrs.	M	7 mos.	Rheumatic heart disease*	ECG	60 to 72	.18	.08 to .10*	85 to 100	18 to 40	.12	High degree with normal P-R	Comp. block vent. tachycardia; then standstill and shift of pacemaker from rt. vent. to A-V node	Atrop. grs. 1/100 4 i.d. abolished attacks for 1 wk. (? specific effect*). Epineph. abolished attacks caused vent. tachycardia	Died in convulsions (7 mos.).
7. Yater and Willius[34]	74 yrs.	M	3 mos.	Arteriosclerosis	ECG	80*	.18*	.08*	120	54*	.08 to .15*	High degree	Aberrant vent. complexes with varying forms. Vent. and cardiac standstill in comp. block	.....	Died in convulsions (3 mos.).
8. Wolferth and McMillan[32]	48 yrs.	F	14 yrs.	.....	ECG	80 to 140*	.16	.10*	100*	30 to 40*	.08 to .10	High degree	2-to-1 heart block shifting to comp. block	Epineph., oculocardiac and vagus reflexes, no effect. Atrop. and amyl nitrite produced part. block. Barium chloride temporarily effective	Died of heart failure (14 yrs.).
9. Carter and McEachern[3]	60 yrs.	M	2½ yrs.	Arteriosclerosis	ECG	53 to 78	.18 to .21	.14	58 to 65	21 to 33	.13 to .16	.....	Aberrant vent. complexes. Left bundle-branch block in nor. rhythm (constant). Rt. bundle-branch block in comp. block on one occasion	Atrop. .25 mgm. s. c., thyroid and oxygen, no effect. Epineph. 0. 5 cc. i. v. caused vent. tachycardia.	Well for 3 mos. (nor. conduction).
10. Cheer and T'Ang[4]	66 yrs.	M	5 mos.	Acute arthritis ? rheumatic ? infectious	ECG	83 to 107	.18	.08	120	18	.08	.....	Vent. arrest to comp. block (4 beats only) to rapid nor. rhythm	Atrop. .25 mgm. daily abolished attacks (? specific effect*)	Well.
11. Weiss and Ferris[29] (Case 1)	54 yrs.	M	10 yrs.	Esophageal diverticulum	ECG	48 to 66	.17 to .21	.08*	39*	18*	.08*	Slight degree at times	Irreg. vent. rhythm	See summary under Pathology	Well with atrop. (gr. 1/120 t.i.d.).
12. Sachs and Traynor[25]	43 yrs.	M	3 mos.	Rheumatic heart disease (?*)	ECG	68 to 88	.16 to .18	.08*	120 to 110*	17 to 19	.10 to .12*	.....	Aberrant vent. complexes with varying forms. Irreg. vent. rhythm	Atrop. grs. 1/30, thyroid, barium chloride and vagal pressure had no effect	Well on discharge (normal conduction).
13. Present case	78 yrs.	F	2 mos.	Arteriosclerosis ? old coronary thrombosis	ECG	60 to 80	.18 to .20	.06 to .08	97 to 68	29 to 35	.06 to .10	.....	Absent Q-wave Lead 4 in comp. block	Ephedr. grs. ¾ 4.i.d. abolished seizures. Atrop. grs. 1/60 t.i.d., no effect	Well in chronic complete block.

* Personal interpretation. New terminology is used in bundle-branch block.

a bar of calcium was found extending across the interventricular septum compressing the bundle of His. It was found histologically that a large portion of the bundle was invaded by fibrous tissue. At no point, however, was the conduction system entirely interrupted for an intact group of fibers was followed in every serial section. There was moderate atheromatosis of the coronary arteries with constriction of some of the smaller branches. Wolferth and McMillan,[32] on gross examination of their heart, found a small area of fibrosis in the septum near the branching of the bundle of His. Histologically, there was interstitial fibrosis with a very slight amount of early calcification involving the main branch below the *A-V* node and both bundle branches. The lesion, however, failed to destroy the bundle completely, for the posterior one-eighth remained intact and appeared normal. There was evidence of coronary sclerosis but grossly the lumina of the vessels were not narrowed.

The pathologic findings in Starling's[27] case are mentioned here because reference to these will be made later. In this case Lewis[17b] found, in addition to thickened calcified aortic cusps, a fibrocalcareous mass fixed to what had probably been the right anterior aortic cusp. This mass formed a saddle over which the bundle of His divided. Histologically, this mass had damaged the lower segment of the main bundle as well as the right and left branches. There was complete destruction of the conducting tissue in this area with replacement by fibrous tissue. The coronary arteries were found to be dilated and markedly sclerotic.

In the case reported by Weiss and Ferris,[29] an esophageal diverticulum was clearly shown to be the causative factor. With distention of the diverticulum by means of a rubber balloon there occurred ventricular standstill accompanied by an Adams-Stokes' attack which was followed by an irregular idioventricular rhythm. With deflation of the balloon the rhythm returned to normal. Epinephrine and ephedrine abolished the seizures but the complete heart block developed as before. There was no ventricular standstill, however, and the idioventricular rhythm became regular. Atropine abolished both the Adams-Stokes' attacks and the complete heart block; the latter being replaced by a partial block as manifested by a moderately prolonged *P-R* interval. From these and other studies the authors concluded that a sensory branch in the adjacent vagus trunk was stimulated by the distention of the diverticulum and a vagovagal reflex ensued which caused a complete *A-V* dissociation.

Case Report. On June 17, 1935, a 76-year-old widowed Lithuanian housewife was admitted to the Boston City Hospital. She had been in good health for many years until 4 weeks before admission. At that time she began to have short sudden attacks of dizziness, heaviness in the head, momentary loss of consciousness with mild twitchings of the extremities followed by fleeting blindness. These attacks were not related to exertion, swallowing, or changes in position. There was no cause to which she could attribute them. The attacks became more frequent until she was having

5 to 7 daily. There were no other central nervous system or cardiorespiratory symptoms.

Aside from the cardiovascular system, the only positive physical findings (including the neurologic examination) were a divergent strabismus of the right eye with bilateral weakness of the internal rectus muscles (old), a palpable liver edge, and a moderate dorsal scoliosis.

Cardiovascular System. The heart was not enlarged or displaced. The rate was 42 per minute and the rhythm regular. The heart sounds were very distant. In diastole there could be heard from one to two muffled sounds and these gave the definite impression of coming at regular intervals. It was also noted that the mitral first sound was occasionally louder than in the preceding beat. A soft systolic murmur was heard over the entire precordium, loudest at the apex. There was slight sclerosis and tortuosity of the peripheral vessels. The opthalmoscopic examination revealed slight vascular changes in the retinal arteries. The blood pressure was 115/40 mm. of Hg.

Laboratory. The red blood cell count was 3,600,000 per c.mm. with a hemoglobin of 68% (S). The white blood cells were normal in number and type. Except for a few white blood cells, repeated urines were negative. The blood N.P.N. was normal. The blood Kahn and Hinton reactions were negative. A lumbar puncture revealed normal pressure and dynamics; there were no cells; the spinal fluid protein was 34 mg.% and the colloidal gold curve 0123210000. The spinal fluid Kahn reaction was negative.

Roentgen Ray Examination. Heart measurements: R.M. 4 cm.; L.M. 8.8 cm.; I.D.C. 30.1 cm.; G.V.B. 4.8 cm. Interpretation: aorta tortuous and sclerotic. Old healed tuberculosis left upper chest. Spine shows marked dorsal scoliosis.

Diagnosis. The patient was, at first, considered to be a case of chronic complete heart block with Adams-Stokes' attacks. The day following admission it was noted that the heart rate had risen to an unusually high level for an idioventricular rhythm. In addition, it was found that during this high rate the muffled diastolic sounds were absent and the heart sounds were loud and distinct in contrast to those found on admission. A paroxysmal heart block was suspected and two electrocardiograms taken on the day following admission revealed the unusual condition present.

Electrocardiographic Tracings. The published electrocardiograms are in general typical of several taken during each phase of the patient's course. Later electrocardiograms taken during chronic complete heart block, however, did show the disappearance of the tendency toward left bundle branch block and the low amplitude of the *Q-R-S* complexes which are present in Figure 3. In addition, a tracing taken in Lead 4 showed an absent *Q* wave which strongly suggests an old coronary occlusion.

The Effect of Atropine and Ephedrine. During a 4-day control period the patient recorded her seizures. There were from 3 to 7 Adams-Stokes' attacks daily with an average of 5 per day. Atropine (grs. 1/60) was then given 3 times daily for 3 days with no effect. Five days later ephedrine (grs. $\frac{3}{4}$) was given 4 times daily and continued for 3 days (no toxic symptoms) with only 1 attack early on the day that this therapy was started. The dose of ephedrine was then diminished to grs. $\frac{3}{8}$ three times a day, but since the patient began having attacks again the ephedrine was increased after 4 days to the former dosage. This was continued for 10 days during which time the patient had no attacks. At the end of this period it was discontinued for the purpose of special electrocardiographic studies with atropine and ephedrine.

At the time when these studies were made it was not realized that the complete *A-V* dissociation had become permanent. When atropine (grs. 1/60) was injected intravenously the auricular rate rose from 72.4 to

77 beats per minute and the ventricular rate rose from 37.5 to 38.7 beats per minute. An acceleration of the ventricular rate in complete heart block after the injection of atropine correlates with Gilchrist's[12] findings. After the injection of ephedrine (grs. $\frac{3}{4}$) intravenously there was no change in either the auricular or ventricular rates.

Outcome. Ephedrine was never resumed and when the patient was last seen in December, 1935, 5 months after the discontinuance of ephedrine, she had had no Adams-Stokes' attacks and her heart had continued to beat within a range of 28 to 35 beats per minute.

COMMENT. When the graphic tracings in this case are correlated with the clinical findings a definite sequence of events is suggested. The patient passed through a period of approximately 6 weeks during which time normal rhythm alternated with complete heart block. There was ventricular standstill with Adams-Stokes' attacks probably during the transition from normal conduction to complete block.

Since atropine did not abolish the Adams-Stokes' seizures during this period it can be concluded with a fair degree of certainty that the vagus played no significant rôle in the fundamental mechanism of this case. The results with ephedrine demonstrate that unusually large doses of this drug are at times necessary to irritate the ventricle sufficiently to enable it to assume an independent pacemaking function in time to prevent the occurrence of Adams-Stokes' attacks.

The basic lesion, apparently organic, was progressive and finally destroyed, at least functionally, an entire section of the bundle of His, thus establishing a chronic complete *A-V* dissociation with an ectopic ventricular pacemaker. With the establishment of a stable ventricular pacemaker, the transitional period between complete auricular and complete ventricular control disappeared. Thus, the immediate cause of the Adams-Stokes' syndrome was abolished and there resulted a spontaneous symptomatic cure.

Form of the Transition. To obtain graphic records in these cases of the transition from one degree of conduction to another is obviously difficult and, for the most part, a matter of chance unless the attacks are frequent or can be induced. None were obtained in the present case. However, in this series, there were 4 cases in which such tracings were obtained.

In Case 2 of Mackintosh and Falconer the change was abrupt from normal conduction to a ventricular standstill which was then followed by an irregular idioventricular rhythm. The transition back to normal was accompanied by a high degree of partial block. Weiss and Ferris found that the abruptness with which the pressure was raised or lowered in the esophageal diverticulum of their patient was the factor determining the presence of partial block in the transition. With a slow change in pressure a partial block developed; with a sudden change there was an abrupt transition from normal conduction to a ventricular arrest. In the case reported by Cheer and T'ang the 4 idioventricular beats were preceded by ventricular

standstill and followed by an abrupt transition to normal conduction with a rapid rate. A tracing published by Wolferth and McMillan showed a 2 to 1 block with a normal *P-R* interval shifting to complete *A-V* dissociation without an intermediate ventricular standstill and presumably without an Adams-Stokes' attack.

From these few graphic observations it would seem that the ventricular standstill and syncope occur after the sudden cessation of normal rhythm and persist until an idioventricular rhythm is established. The last observation, however, shows that the transition from normal to an idioventricular rhythm by means of an intermediate high-grade block may not be accompanied by ventricular standstill or an Adams-Stokes' attack. There is also the possibility of ventricular standstill with symptoms occurring during the course of the idioventricular rhythm. The return from complete heart block to normal conduction is variable but probably not accompanied by asystole or syncope.

Clinical Features. Several clinical facts in recurrent complete heart block which are important diagnostically and therapeutically should be emphasized. The possibility arises that paroxysmal complete heart block may not be an uncommon precursor of complete heart block. Consequently, a paroxysmal complete heart block should be suspected in all cases of Adams-Stokes' syndrome, particularly early in the disease. The finding of a relatively high pulse rate in a case of complete heart block is strong evidence that an intermittent block may exist. The periodic appearance and disappearance of diastolic muffled auricular systolic sounds which may be accompanied by marked differences in the intensity and distinctness of the heart sounds furnish valuable clinical clues for the diagnosis of this condition. Electrocardiograms must be taken to establish a definite diagnosis. Although certain drugs may abolish the Adams-Stokes' attacks in these cases, the possibility of the establishment of a permanent complete heart block with the spontaneous disappearance of the syncopal seizures should be kept in mind.

Pathogenesis. There are various factors capable of causing variations in auriculoventricular conduction. All of these are not clearly understood. That complete *A-V* dissociation with an idioventricular rhythm can be established through vagal stimulation alone has been clearly shown in the case studied by Weiss and Ferris. That vagal stimulation can also be a contributory factor in the presence of organic disease is strongly suggested in Starling's case by the association of ventricular standstill and Adams-Stokes' attacks with swallowing, and the abolition of the seizures with atropine. Lewis pointed out a significant fact in this case, *viz.*, that although results with atropine may give evidence that the vagus is responsible for the occurrence of transient complete block, it cannot be definitely concluded from this test that the vagus is the only factor involved. The vagus factor is again strongly suggested in Case 2 of Mackintosh

and Falconer since relief of symptoms was obtained with atropine. The marked alternating changes in *A-V* conduction which occasionally accompany the two phases of Cheynes-Stokes respiration are also best explained on a vagal basis. Pathologic involvement of the vagus nerve has in itself been given as a cause of heart block in several cases.[14,20]

Gallemaerts[9] reported a remarkable case in which a transient complete heart block was definitely associated with orthostatic changes. His patient developed a temporary complete block with Adams-Stokes' attacks when the position was changed from recumbent to sitting or standing. The only other abnormality of conduction in this case was the constant finding of a slightly prolonged *P-R* interval (0.24 second). Atropine had no effect. Lutembacher[18] reported a similar case in which a partial heart block was associated with orthostatic changes. Alexander and Bauerlein[1] reported a case in which an irregular rhythm with a rate of 42 beats per minute and a *P-R* interval ranging from 0.24 to 0.40 second in the supine position is changed to a regular rhythm with a rate of 94 and a *P-R* interval of 0.24 second when the patient is within approximately 15 degrees of the vertical position. The attacks of dizziness and the high degree of partial heart block have been relieved by atropine. Such findings offer much in the way of interesting speculation as to the factors responsible for fluctuations in auriculoventricular conduction.

A recurrent transient degree of inflammation in the bundle of His may possibly best explain the fluctuations in auriculoventricular conduction in Cases 10 and 12. In view of the calcification found at the aortic orifice at postmortem, subacute inflammation, although present, is not necessary to explain the clinical picture in Case 4. From the clinical findings in these cases and the postmortem findings in Case 4 the etiology of any inflammatory changes is not clear. The assumption of a rheumatic etiology is possibly warranted because of indirect evidence that it may have existed in these cases and because of the known fact that this disease has a particular affinity for the conduction system. However, from the evidence at hand this assumption cannot be made with any degree of assurance and, as a result, it seems only safe to say that complete heart block alternating with normal rhythm *may* result from infection. Furthermore, whether or not recurrent transient degrees of inflammation can cause this condition without there being another factor damaging the bundle of His, as in Case 4, can only be determined by further pathologic evidence in such cases.

There is an additional and larger group among these cases in which another common etiologic mechanism may be postulated (Cases 1, 2, 3, 5, 7, 9 and 13). This group for the most part includes patients of advanced years who have direct or indirect evidence of arteriosclerosis.

Norris in his discussion of Earnshaw's[28] case suggested the basis for the ensuing explanation of the fluctuating function of auriculoventricular conduction in this group. These cases probably have an organic process partially destroying a portion of the A-V node or main bundle. That the organic lesion in this group is usually either a fibrocalcareous mass at the base of the aortic valve, or an area of fibrosis due, most likely, to a coronary infarction of greater or less degree, is made quite probable by the fact that such findings are not uncommon in the hearts of individuals of this age group. In addition, these lesions are among the most frequent pathologic findings in complete heart block and in the present group. The literature on complete heart block due to fibrocalcareous lesions has been recently summarized by Yater and Cornell.[33]

The tone of the remaining undamaged conducting fibers determines the degree of auriculoventricular conduction. As long as the tone of these fibers is maintained by adequate nourishment they are able to transmit auricular impulses in a normal manner. However, as soon as changes in the local circulation occur which deprive these fibers of adequate metabolic exchanges, a partial or complete block develops. The extent of the block will depend upon the amount and duration of the nutritional impairment. Géraudel[10] in recent years has offered pathologic evidence that certain cases of heart block may be on a circulatory basis. He reports 2 cases of complete heart block, one of which was intermittent, in which serial sections of the conducting system showed no lesion. In both of these cases, however, he demonstrated a definite arteriosclerotic narrowing of the artery leading to the bundle of His.

If the organic lesion is progressive a section of the main conducting system will eventually be destroyed and a permanent complete heart block will be established. In this connection, however, as well as in the chronic block which developed in the present case, it must be remembered that discrepancies exist between the function of auriculoventricular conduction and the extent of the histologic damage in the bundle of His. Apparently permanent and, certainly, long periods of complete heart block have been observed in cases which showed partial or no destruction of the conducting system.[10,15,16,21–23]

Summary. 1. The literature of recurrent complete heart block alternating with normal conduction and accompanied by Adams-Stokes' syndrome has been examined critically. Of 20 potential cases discovered in the literature, 12 have been accepted as complying with the criteria established. The important clinical, pathologic, and electrocardiographic data of these cases have been summarized.

2. A case, a woman aged 78, with Adams-Stokes' syndrome, is presented in which, as shown by electrocardiographic evidence, complete heart block alternated with normal rhythm and conduc-

tion. The results with atropine demonstrated that the changes probably occurred independent of any vagus effect. This case ultimately developed a chronic complete block with the spontaneous disappearance of the syncopal attacks.

3. The form of the transition from one degree of conduction to another, as shown by graphic tracings, is summarized.

4. The practical diagnostic and therapeutic considerations of this condition are emphasized.

5. The pathogenesis of paroxysmal complete heart block is discussed. It is probable that the majority of cases are on an arteriosclerotic basis and that either a fibrocalcareous mass or fibrosis due to coronary sclerosis partially damages the bundle of His. The fluctuating character of the conduction in these cases is probably determined by temporary variations in the local circulation to the remaining intact fibers.

It is a pleasure to acknowledge my appreciation to Dr. Soma Weiss, of the Boston City Hospital, and Dr. Paul D. White, of the Massachusetts General Hospital, for their interest and advice in the preparation of this manuscript.

Addendum.—While this report was in press an additional case has been observed. A 57-year-old male was admitted to the Massachusetts General Hospital, complaining of 3 to 10 fainting attacks daily for a period of 2 months. Until this illness he had been in good health for many years. There were no cardiovascular symptoms. Physical examination was negative except that at times a slow heart rate (35 to 45 beats per minute) accompanied by auricular sounds was present. The electrocardiograms showed complete heart block (Q–S 0.07) alternating with normal rhythm (P–R 0.17, Q–S 0.07). Repeated trials of carotid sinus stimulation during normal rhythm caused slight sino-auricular slowing without alteration in the P–R interval, but failed to produce auriculoventricular block. While on the ward his heart rate fluctuated between 35 and 100 beats per minute. These fluctuations in rate and his attacks became progressively less frequent. At the end of 2 weeks a heart rate of 35 to 40 per minute seemed permanently established and his attacks ceased. When seen a month after discharge his heart rate was 35 beats per minute and there had been no recurrence of the attacks.

In a recent report Gilchrist (Brit. Med. J., **1**, 203, 1937) states that he has observed 8 cases of this type. Only 2 of these are reported in detail.

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VAGAL REFLEX IRRITABILITY AND THE TREATMENT OF PAROXYSMAL AURICULAR TACHYCARDIA WITH IPECAC.

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Paroxysmal auricular tachycardia frequently occurs in subjects without demonstrable cardiac lesions and with a normal or fair degree of cardiac reserve. Even in such cases effective treatment is of practical importance, not only because the unexpected appearance of the attacks often results in demoralization of the patient, but also because the condition often interferes seriously with his occupation unless the attacks can be promptly checked.

A number of therapeutic measures are alleged to have beneficial effects in the treatment of paroxysmal auricular tachycardia. White[10] states, however, that "the very fact that there are many different drugs and therapeutic measures recommended for the immediate treatment of paroxysmal tachycardia shows that there is not one really satisfactory treatment." The purpose of this communication is 1, to demonstrate that ipecac is a suitable agent for the relief of the attacks, and 2, to analyze the underlying principle in the treatment of paroxysmal auricular tachycardia.

Among the therapeutic measures advocated are rest, induced sleep, bending, turning of the head, stooping with the head low, pressure over the "vagus," the carotid sinus or the eyeballs, and induction of "Valsalva" or "Müller" experiments. Digitalis, strophanthin, quinine, quinidine, morphine, apomorphine, acetylcholine and acetyl-β-methylcholine are some of the drugs used. Any of these measures may be effective in one patient but not in another,

and a measure previously beneficial may have to be intensified in order to abolish subsequent attacks, or may even become ineffective.

That the vagus nerves play an important rôle in paroxysmal auricular tachycardia has been appreciated for some time. Practically all measures capable of abolishing paroxysmal auricular tachycardia possess also the characteristic of increasing the cardiac vagal tone. It is known that paroxysmal auricular tachycardia results from the sudden activation of an ectopic focus in the auricle, with or without circus movements. Such an ectopic auricular pacemaker, by its faster inherent rate, gains control of the cardiac cycle. In order to reëstablish normal sino-auricular rhythm, one can therefore attempt to reduce the excitability of the auricular myocardium with drugs such as quinine or quinidine. These substances, however, are more effective in preventing the attacks than in abolishing them. The most effective way to eliminate the activity of the ectopic focus and to reëstablish normal rhythm is through the induction of powerful vagal inhibition of the auricles. Hence, the problem of the treatment of paroxysmal auricular tachycardia is to a large extent identical with the problem of increasing the cardiac vagal tonus.

The Use of Ipecac. Some 10 years ago, in the search for a simple and effective vagal stimulant for the treatment of paroxysmal auricular tachycardia we selected ipecac, since it is known to contain several alkaloids with emetic effect, which act both peripherally and centrally.[2b]

We have used ipecac in 11 cases,* ranging in age from 16 to 54. In 4 cases rheumatic and in 1 case hypertensive heart disease was the underlying cause of the attacks, and in 6 cases no organic heart disease could be detected. The diagnosis of paroxysmal auricular tachycardia was usually confirmed by means of electrocardiographic tracings. In addition to these patients personally treated, we know of a large group of patients treated successfully by other physicians.

Dosage. From 1 to 4 drams (4 to 16 cc.) of syrup of ipecac administered orally proved to be the minimal effective dose. If an initial dose of 1 to 2 drams produced no vomiting or the desired effect, the dose was repeated in 45 minutes. Fresh and potent preparations should be used in view of the fact that considerable variation exists in the potency of various specimens of the syrup tested. While we have not used other ipecac preparations, they may well be equally efficacious.

Results. In all our cases this medication proved to be effective. In 1 case, however, doses of 1 and 2 drams, which relieved several attacks while the patient was under our observation, were later claimed to be ineffective. The physician reporting this lack of response failed subsequently to administer larger amounts; hence one

* Since this paper was submitted for publication we have treated 3 additional patients successfully with ipecac. In 2 of these patients no organic heart disease was present and the attacks followed surgical manipulation of the uterus. In the third patient rheumatic heart disease with mitral stenosis was present.

cannot state whether or not the drug failed. We know of 2 additional cases treated by others in which it was claimed that the medication was ineffective. Our observations indicate that, just as with other drugs used in the treatment of paroxysmal auricular tachycardia, the dosage may have to be raised with progressive severity of the seizures in the same patient, and the effective dosage varies considerably for different patients.

Following the administration of the effective dose, nausea and vomiting usually developed within 10 to 45 minutes. Simultaneously, preceding or following the retching or vomiting, the heart rate slowed down rather abruptly, and finally changed to normal sinus rhythm. We have had opportunity to hear the rapid heart sounds and to feel the rapid pulse change rather abruptly to a rate of 40 to 60, associated with loud heart sounds, full pulse and some sinus irregularity ("vagal beats"). One to 2 minutes thereafter a somewhat more rapid and a regular sinus rhythm became established. The fact that vomiting was induced but the attack was not abolished does not necessarily indicate failure of the medication. We have observed instances in which mechanically induced vomiting or vomiting induced with 1 dram (4 cc.) of syrup of ipecac failed to abolish the tachycardia, while subsequent administration of 2 drams (8 cc.) or more stopped the attack. Our experience indicates that usually the dose should be raised until vomiting occurs, but the minimal emetic dose may still be inadequate for the reëstablishment of sinus rhythm. In some cases, local irritation from the stomach precipitates vomiting and eliminates the medication before it can be absorbed. For reëstablishment of sinus rhythm the more powerful combined peripheral and central vagal stimulation is often required, and this can be induced only with higher dosage. Such higher dosage is often followed by a sensation of nausea and other evidences of parasympathetic stimulation of from 1 to 4 hours' duration.

Once the dosage of ipecac is established, it can be used by the patient without hospitalization or medical supervision. This not only represents an economic advantage, but is helpful in alleviating the constant dread of attacks and of isolation from a physician. The fact that the nausea and vagal stimulation in general last for some time, depending on the dosage, makes the effect of the drug more secure. Measures which stimulate the vagus for a short time frequently slow down the heart only temporarily and they fail to abolish the attack regularly. With the exception of weakness accompanying the nausea, and mild diarrhea, no untoward effects have been observed in the patients treated personally. We know of a patient treated in another institution who was relieved of an attack of paroxysmal auricular tachycardia but subsequently developed peritonitis. Autopsy revealed a ruptured subdiaphragmatic abscess. In this very unusual case it was assumed that the vomiting was responsible for the rupture of the previously unrecognized

abscess. Since the drug is administered orally, its emetic effect is a safeguard against toxic overdosage.

We have made no study of the efficacy of ipecac as compared with other measures. In all our cases, however, some of the other methods, such as calisthenic motions, pressure on the carotid sinus and over the eyeballs, and mechanically induced vomiting, had failed. In addition, drugs such as digitalis, morphine and acetyl-β-methylcholine had also been used in some of the cases before ipecac was administered. Our experience with acetyl-β-methylcholine is similar to that of Starr.[5] In several instances the dosage had to be raised to a level which was associated with alarming transient manifestations. We believe, however, that ipecac should be used only after the simpler physical measures have failed.

It should be recalled that drugs such as morphine, apomorphine, digitalis and acetyl-β-methylcholine, which frequently abolish paroxysmal auricular tachycardia, often produce nausea or vomiting. This emetic action depends in part upon vagal stimulation. Thus in all these measures the basic underlying mechanism may well be the same, namely, vagal stimulation.

Mackenzie[3a] makes no mention of ipecac in the treatment of paroxysmal tachycardia. In reporting Case 68, however, a 27-year-old man suffering from "paroxysmal tachycardia probably due to auricular flutter," Mackenzie mentions that this patient had been using wine of ipecac for some years before he learned about it in 1910.[3b] Mackenzie subsequently observed the efficacy of this treatment in the patient. It is almost certain that this case was an instance of paroxysmal auricular tachycardia rather than of auricular flutter. Schilder,[4] in 1934, advocated the induction of vomiting in the treatment of paroxysmal auricular tachycardia. He has successfully used a 1% solution of copper sulphate, of which he administered a "spoonful" at 5-minute intervals until the onset of vomiting. He mentions that at times one observes beneficial results with ipecac. These are the two casual remarks on the use of ipecac in paroxysmal auricular tachycardia that we were able to find in the literature.

Case Reports. CASE 1.—A surgeon of 54 was seen in consultation in May, 1932, because of increasingly frequent attacks of paroxysmal tachycardia. He had had no important infections in youth except typhoid fever at the age of 15 and severe sore throats, for which his tonsils were removed when he was 40. At college it was discovered that he had a heart lesion which, when he was first seen by us in 1932, was found to be rheumatic aortic regurgitation with moderate cardiac enlargement. On Roentgen ray examination the aorta was found to be greatly dilated, probably as a result of the aortic regurgitation. In spite of the cardiac lesion he had always been very active, both professionally and as a sportsman, being up to the present time a cup-winning golfer. He had had his first attack of paroxysmal tachycardia $8\frac{1}{2}$ years ago, and several of these attacks had occurred at intervals of several months or years. When seen the first time he was having an attack of rapid, regular heart action at a rate of 160, which had persisted for 24 hours; no previous attack had lasted for more than 8 hours. Electrocardiogram

showed paroxysmal tachycardia with left axis deviation and slight slurring of the *Q–R–S* complexes. The attack ended spontaneously a few hours later.

During the next 3 years various measures were tried to prevent the attacks—quinidine (from 3 to 9 grains a day), digitalis, sedatives, purine derivatives; reduction of coffee, tea, tobacco, alcohol and golf; removal of foci of infection; colonic irrigations; and the study of basal metabolism and possible allergic factors by skin tests. In October, 1934, he began to have anginal pain on exertion and this became so uncomfortable whenever attacks of paroxysmal tachycardia were present that it was necessary to give him morphine with each one. The attacks lasted on an average for 13 hours, and he was finally put to bed for several weeks to regain cardiac reserve. Following this, he was able to continue his work, with very restricted exertion. The attacks were frequently repeated, one lasting 70 hours when he was on a West Indian cruise. His plans were disrupted by these attacks and he was continually apprehensive lest one appear. Attacks frequently came on early in the morning, required morphine and the installation of a trained nurse in the home, and, at best, would keep him away from his practice for from 1 to 5 days. It became impossible to rely on quinidine because of the onset of tinnitus and a sensation of fullness in the head when only 3 grains a day were given.

On April 1, 1935, an attack started after breakfast and he was instructed to induce vomiting by putting his finger down his throat, a procedure which he could do with ease. Vomiting occurred but the tachycardia persisted. Stimulation of the carotid sinus was attempted with no effect as far as the tachycardia was concerned, but with the production of a rather disturbing attack of scotoma, hemianopsia, and slight numbness of the right arm lasting about 20 minutes. Three doses of mecholin, 7, 7 and 15 mg., given subcutaneously at 15-minute intervals, caused flushing of the face, pressure in the chest, thumping of the heart and a drop in blood pressure from 135 mm. to 80 mm. systolic. It was thought unwise to continue with larger doses since the beneficial effect from mecholin is usually secured coincidentally with the fall in blood pressure. Syrup of ipecac was then suggested. Two drams were given, 30 minutes later 4 drams, and 15 minutes thereafter 8 drams. After several waves of severe nausea active vomiting and retching occurred, and at this moment the attack stopped, the pulse rate returning to 80.

On May 2, 1935, an attack started which was terminated in 20 minutes by the patient himself, who immediately took 4 drams of ipecac. Retching continued for 45 minutes. On June 1 this was repeated, the attack being ended at 7 o'clock, 10 minutes following onset, by the use of 4 drams, and he was able to operate at 9 o'clock.

Since that time ipecac has been used successfully by this patient approximately 40 times. The demonstrable saving of heart beats in the first year was estimated as being in the neighborhood of a million. In the presence of organic heart disease the importance of this is obvious.

Case 2.—A 22-year-old theatrical worker entered the hospital in February, 1927, having been admitted before on several occasions with paroxysmal auricular tachycardia, as indicated by the electrocardiograms. The physical examination revealed no abnormality of the cardiovascular system. Previous attacks were usually relieved by stooping. The present one lasted for 6 days and could not be relieved by physical measures. Quinidine, grains 3, every 3 hours for 6 doses, and intravenous strophanthin, grains 1/120, failed. Spontaneously induced vomiting also remained ineffective. Three drams of syrup of ipecac produced severe nausea and vomiting and 50 minutes later the attack ceased. The heart rate dropped from between 210 and 220 to 80. Two months later the patient returned with a similar attack. Administration of ipecac again promptly relieved the tachycardia.

CASE 3.—A 38-year-old housewife was observed in 1928 with an "attack of palpitation." She had had similar attacks on several occasions, lasting from several hours to several days, and associated with precordial distress, radiating to the left arm. Physical examination (including the arterial pressure) was normal. The patient was observed during several of these attacks. Electrocardiograms revealed paroxysmal auricular tachycardia with a rate of 200 or over. The Q–R–S interval was 0.06 second and the T waves were upright in all leads. Induced vomiting and morphine (grains $\frac{1}{8}$) subcutaneously were ineffective. Full digitalization of the patient produced nausea and vomiting, and with the onset of these symptoms the attack stopped. The patient continued to vomit and remained nauseated for 24 hours. An electrocardiogram taken subsequently revealed sinus rhythm with a rate of 50. A subsequent attack of tachycardia was relieved one-half hour after the administration of 2 drams of ipecac. The change in rhythm occurred simultaneously with the onset of retching.

CASE 4.—A 16-year-old student was first admitted in 1930, and again on numerous occasions with attacks of rapid heart rate associated with mild precordial pain, dyspnea, and feeling of coldness in the hands and feet. These attacks came on day or night. There was a history of rheumatic fever. Physical examination revealed malar flush; the apex impulse was prominent with systolic thrill and murmur over apex; the maximal left border was 11 cm. in the fifth space. Roentgen ray examination revealed rheumatic deformity of the heart. The arterial pressure was 90/60. Electrocardiograms on several occasions indicated paroxysmal auricular tachycardia with a rate of 200 or over. Following the attacks there was a sinus rhythm with a rate of 70 to 80, Q–R–S interval 0.12 second, P–R 0.24, high P_1 and P_2.

The patient was observed in several attacks. The earlier ones were relieved by straining, bending or other bodily calisthenics, but later ones failed to respond to these measures, or to carotid sinus pressure or induced vomiting. One or 2 drams of syrup of ipecac regularly relieved these attacks within 15 to 30 minutes.

In 1935, the patient was observed by a physician who reported that 1 dram of ipecac, which had previously been effective, now failed to control the attacks. No larger dose of ipecac was administered; instead, the efficacy of acetyl-β-methylcholine was tested. On one occasion a total of 52 mg. of acetyl-β-methylcholine was given in divided doses. Following this, rather alarming symptoms developed, associated with transient cardiac standstill, and simultaneously the attack stopped.

CASE 5.—A 19-year-old student was observed in November, 1933, complaining of pain in the left chest of 2 days' duration. Physical examination revealed no abnormality of the cardiovascular system. Blood pressure was 120/70. During attacks the heart rate was 200 to 220 per minute and electrocardiogram showed paroxysmal auricular tachycardia. Two attacks were relieved by pressure on the eyeballs. This measure, as well as pressure on the carotid sinus, was ineffective in a third attack. Administration of 2 drams of syrup of ipecac abolished the attack in 18 minutes. Ipecac has been used in subsequent attacks, with relief.

CASE 6.—A 23-year-old man entered the hospital in November, 1932, with the complaint of attacks of forceful, rapid heart beat during the past 6 years. These attacks were precipitated mainly by nervous strain and usually started with a sensation as if the heart was "flopping over." The rate became rapid, "about 200." Simultaneously there was a sensation of light-headedness, of vertigo, of a lump in the throat and of choking The attacks ended abruptly after 6 to 12 hours; in some he experienced precordial pain, radiating to the back. Physical examination was negative. The patient was not observed in an attack while in the hospital. Between

attacks the electrocardiogram was normal except for the diphasic T_3. The clinical diagnosis of paroxysmal auricular tachycardia was made and the patient was advised to take 1 or 2 drams of syrup of ipecac in case of an attack. During the following 14 months he had 6 attacks, each of which was promptly relieved within one-half to three-quarters of an hour after taking ipecac.

Case 7.—A 29-year-old technician was observed between 1931 and 1934. He had a history of rheumatic fever, and complained of attacks of palpitation, rapid heart action and precordial distress. Physical examination revealed an aortic insufficiency with enlargement of the heart. The blood pressure was 160 to 170 over 70 to 80 mm. Hg. The blood serologic tests were negative. Electrocardiograms showed paroxysmal auricular tachycardia. In March, 1931, the patient developed an attack of paroxysmal auricular tachycardia with a rate of 180 to 210, which lasted for several days. Various physical manipulations, as well as the administration of quinidine, gave no relief. Oral administration of 2 drams of syrup of ipecac subsequently induced vomiting in 30 minutes and simultaneously normal sinus rhythm was reëstablished.

In July, 1935, the patient entered the hospital with a similar attack, which had lasted over 12 hours. Fifteen minutes after the administration of 1 dram of syrup of ipecac he became nauseated and vomited. Simultaneously the heart rate slowed down for a few minutes, but thereafter the tachycardia returned. About 15 to 17 minutes after another dram of syrup of ipecac, the patient vomited again, and simultaneously normal sinus rhythm returned. An electrocardiogram revealed sinus rhythm of 76 with premature auricular and ventricular beats. QRS was 0.12 second; P–R 0.28 second.

Case 8.—A 20-year-old girl entered the hospital on December 15, 1931, complaining of attacks of palpitation and dyspnea. For 12 years she was known to have rheumatic heart disease. During the past 2 years she had experienced attacks of rapid heart rate associated with palpitation, dyspnea and a sensation of faintness. The heart was enlarged. There was a double murmur over the aortic area. The blood pressure was 150/0 mm. Hg. The blood serologic tests were negative. Among the various manipulations, pressure over the carotid sinus was the only one to relieve the attack. On two occasions the attacks were relieved 17 and 22 minutes, respectively, after the oral administration of 2 drams of syrup of ipecac. Relief coincided with the onset of severe nausea and retching.

Case 9.—A 52-year-old laborer entered the hospital on January 17, 1932, with the history of shortness of breath of 9 months' duration and attacks of palpitation for 3 months. The heart was enlarged to the left and to the right. No evidence of valvular lesions was elicited. The arterial pressure was 180/100. He was observed in two attacks, which were revealed by electrocardiogram to be paroxysmal auricular tachycardia. Both attacks were relieved one-half to 1 hour after the administration of 2 drams of syrup of ipecac. Following this relief the electrocardiogram showed sinus rhythm with left ventricular preponderance. The rate was 94, the P–R interval 0.16 second and the QRS interval 0.07 second. The T waves were upright in all leads.

Case 10.—A 48-year-old housewife suffered from pernicious anemia associated with attacks of palpitation. On physical examination the heart was normal; the blood pressure was 110/80 mm. Hg. The electrocardiogram indicated that the attacks were paroxysmal auricular tachycardia. The patient was observed in one of her attacks, which lasted for 4 hours. She became nauseated and vomited 38 minutes after the oral administration of 2 drams of ipecac. At the same time the heart rate dropped from between 200 and 210 to from 80 to 84 and the patient was relieved.

CASE 11.—A 19-year-old nurse was observed in May, 1931. She complained of attacks of precordial distress and palpitation. Physical examination was negative. During the attacks the heart rate was over 200 per minute. Twelve minutes following the administration of 2 drams of syrup of ipecac the patient vomited and the heart rate dropped to 64, later rising to from 80 to 84 per minute. Four subsequent attacks were relieved by ipecac.

The Relation of the Irritability of the Vagal Reflexes to the Principle of Treatment of Paroxysmal Auricular Tachycardia. Clinical and experimental evidence indicates that much variation exists in the tonus of the individual reflexes of the autonomic nervous system, both in health and in disease. The irritability and the motor effects of the same autonomic reflex exhibit considerable variation in normal persons. Increased motor tonus within the sympathetic nervous system often depends on hyperactivity of individual reflexes of the autonomic nervous system, rather than of the entire system.[1] In analyzing certain clinical manifestations of the hyperactive carotid sinus reflex, it has been stated: "What we consider as the vagal or other medullary center is, therefore, a condensed and busy relay station with some constant, but also with numerous continuously changing activities of sensory and motor connections. Some of these active reflexes are innate; some develop with the evolution of the body; others are the result of training; and still others develop with disease."[7]

Increased cardiac vagal tone depends on increased activity of vagal reflexes, rather than on local stimulation of the vagal motor nerve endings. The sensory-vagal reflexes influencing the heart are numerous. Patients have been observed in whom temporary cardiac standstill could be induced by a slight degree of stimulation of afferent endings of the intercarotid nerve within the carotid sinus, of trigeminal nerve endings within the orbit, of afferent vagal nerves in the throat, esophagus or stomach, or of afferent pleural nerves.[1,6,7,8] In these patients hyperactivity of one of these autonomic reflexes was usually associated with a normal state of other reflexes. In a study of the carotid sinus reflexes it was also observed that even within the group of subjects with "normal responses" marked variations existed in the degree of cardiac slowing which could be induced by stimulation of the sinus. In some subjects, stimulation failed to induce inhibitory influence on the heart; in others, the slowing was slight and transient; and in still others it was marked. Moreover, the response of one carotid sinus frequently differed from that of the other.[1,7] A similar variation in the reflex response exists in the behavior of the oculovagal reflex (Aschner-Dagnini phenomenon).[6]

Another instance of variation in vagal reflexes can be found in the behavior of vomiting. It is known that vomiting is always a reflex act, depending on peripheral stimulation of the medullary vagal

centers, on a primary increase of the excitability of these centers, or on a combination of these two factors.[2a] The act of vomiting is often associated with hyperactivity of a number of vagal and parasympathetic reflex manifestations. The extent of these vagal manifestations, however, varies considerable depending not only on the etiology and mechanism of various types of vomiting, but also on the innate character of the autonomic nervous system of the subject. Both in animals[2a,2c] and in man,[1,6] the same type of peripheral and central stimulation of the vagus system produces various degrees of increase in the cardiac vagal tonus. Some of the centrally acting vagal stimulants, such as morphine, apomorphine and medullary anoxia, have abolished attacks of paroxysmal auricular tachycardia in some but not in other subjects. In a study of vasomotor collapse induced with sodium nitrite, it has been observed that in normal subjects cerebral ischemia induces varying degrees of cardiac inhibition. In some individuals no vagal inhibition was observed.[9] Thus central vagal response to anoxia also shows marked individual variations. These considerations, as well as the experience we have gained with the use of central and peripheral emetics in the treatment of paroxysmal auricular tachycardia, indicate that the degree of cardiac vagal inhibition does not necessarily parallel the vagal action on the gastro-intestinal canal. One type of emetic may be capable of stopping an attack of paroxysmal auricular tachycardia, while another is ineffective.

Central vagal inhibition of anoxemic origin plays a rôle in the spontaneous cessation of the attacks. Thus we have had the opportunity to observe a 37-year-old patient without organic heart disease whose attacks during the past 25 years never lasted longer than from 2 to 8 minutes. With the onset of an attack her normally low arterial pressure of 90 to 100 mm. Hg systolic and 64 to 70 mm. Hg diastolic rapidly fell to between 40 and 60 mm. The attack of tachycardia of from 150 to 160 per minute was associated with dizziness, weakness, dimness of vision and profuse perspiration. When these manifestations became pronounced, and the blood pressure could barely be measured, she experienced sudden slow palpitation for from 10 to 20 seconds. The heart rate simultaneously dropped to from 30 to 40 per minute and thereafter a normal sinus rhythm of 80 to 90 per minute became reëstablished. Here we are dealing, then, with a self-regulatory therapeutic function of the body. The tachycardia results in reduction of the cardiac output, which, in turn, leads to medullary ischemia (vasovagal syncope),[9] causing central vagal stimulation and return of the sinus rhythm.

These examples clearly indicate, then, that the sensory cardiovagal reflex nerve endings and their central synapses can be stimulated in a number of ways. The effectiveness of the stimulation depends, among other factors, on the normal 'activity" and "tonus" of the specific reflex in the given case. If a reflex is

not active, stimulation may be ineffective. In a healthy person, some of the vagal reflexes may be ineffective, others normally active, while others may be relatively hyperactive. Thus in an individual with an active carotid sinus reflex, stimulation of the sinus will be an effective measure for inducing asystole, while stimulation of other afferent pathways of the vagus may be entirely without effect. We have demonstrated that stimulation of the carotid sinus will abolish attacks in one group of patients with paroxysmal auricular tachycardia, but it will remain ineffective in another group.[7] The more developed the carotid sinus-cardiovagal reflex is, the more effective is the stimulation. This can be illustrated by a case in which there was the unusual coexistence of a hyperactive carotid sinus reflex and paroxysmal auricular tachycardia. Through the courtesy of Dr. H. L. Blumgart we had the opportunity to observe a 57-year-old patient who, during the past 20 to 25 years, has had attacks of palpitation, in recent years followed by giddiness and finally by syncope associated with rapid heart rate. In the beginning the attacks occurred once in 6 months and lasted for only 15 minutes, but they have gradually increased in frequency and in duration. During one of the attacks observed, the cardiac rate was 200 per minute. The rhythm was regular. The heart was normal in size. The arteries were sclerosed. There was no venous engorgement, cyanosis or peripheral edema. Pressure on either carotid sinus, but especially on the right, reduced the rate to 80. Continued pressure on the right sinus finally resulted in complete asystole, and in a rapid fall of the blood pressure to 80 mm. Hg. The patient felt faint and dizzy and his respirations became slow. Thus in this patient, as a result of the coexistence of paroxysmal tachycardia and hyperactive carotid sinus reflex, it was possible to change the cardiac rate of 200 to a state of asystole.

The marked individual variations in reflex excitability of the sensory-cardiovagal reflexes are, in our opinion, to a large extent responsible for the variability of response to the different measures advocated in the past for the treatment of paroxysmal auricular tachycardia. In view of the variations in the response of vagal reflexes, as well as in the central synapses, such variations in response are inevitable. As we do not possess methods to determine which type of sensory-vagal reflex is most effective for increasing the cardiovagal tone in a given case, for practical purposes it remains essential to test the efficacy of several types of peripheral or central vagal stimulation.

Summary. 1. Ipecac is a useful agent in the treatment of paroxysmal auricular tachycardia.

2. In 11 cases attacks were relieved following the oral administration of doses of from 4 to 32 cc. (1 to 8 drams) of syrup of ipecac.

3. The pharmacologic principle underlying this method of treatment and the considerations to be observed in its application are described.

4. The relation of the physiologic state of the autonomic nervous system, and particularly of the sensory-vagal reflexes, to the effective treatment of paroxysmal auricular tachycardia is discussed. The more powerful the vagal stimulus applied and the more increased the tonus of the specific reflex, the greater is the probability of therapeutic success.

5. The pronounced variations in the tonus and in the irritability of the various cardiac inhibitory reflexes are the basic cause underlying the variability of effectiveness of measures used in the treatment of paroxysmal auricular tachycardia.

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ADULT SCURVY; STUDY OF THE URINARY OUTPUT OF CEVITAMIC ACID.*

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Since 1928, great strides have been made in the purification, isolation, and synthesis of vitamin C.

Szent-Gyorgi's[23a,b] original discovery of a strongly reducing substance in the adrenal cortex of oxen, as well as in oranges and cabbages, was really the forerunner of the present researches. Szent-Gyorgi extracted this reducing substance from the adrenal and regarded it as an acid of the hexuronic series. Tillmans, *et al.*,[24,25] trying to differentiate between true and artificial lemon juice, found that 2 to 6 dichlorphenol-indophenol was decolorized only by true lemon juice. They subsequently made the suggestion that the distribution of Szent-Gyorgi's hexuronic acid in nature coincided with the distribution of vitamin C. Szent-Gyorgi and

* Read, in abstract, at a meeting of the Section on Medicine, of the New York Academy of Medicine, May 19, 1936.

Svirbely[22a,b] then succeeded in curing guinea-pigs of scurvy with hexuronic acid. Finding that hexuronic acid also reduced dichlorphenol-indophenol prompted them to suggest that the acid was identical with the reducing substance found by Tillmans in lemon juice. King and Waugh[14a,b] stated that they obtained a crystalline substance from lemon juice which showed antiscorbutic properties and was similar in chemical and physical properties to hexuronic acid. The final establishment of hexuronic acid as vitamin C and the synthesis of the compound was established first by Haworth[10] and secondly by Reichstein, Grussner, and Oppernauer.[18]

In the last 3 years much work[5,13,17] has been done on the urinary excretion of vitamin C, following Harris, Ray, and Ward's[8] studies in 1933.

In a person whose diet has been adequate in vitamin C, the quantity of urinary excretion of the vitamin, or as it is now called, cevitamic acid, is constant from day to day and averages about 15 to 33 mg. daily; Ahmad[2] 23 to 35 mg., Hawley[9] 15 to 28 mg., Harris and Ray[8] 30 to 33 mg. The greater the intake of vitamin C, the greater is the urinary excretion. If a test dose of 600 mg. is given, there is considerable rise in excretion for the next 24 hours. If excessive amounts of vitamin are given for a considerable length of time, most of the excess is stored chiefly in the adrenals, pituitary, and liver, the remainder excreted until a point of complete "saturation" is reached. When this occurs, about 80% of all additionally ingested vitamin C is excreted, the fate of the other 20% being unknown. Thus the amount of test dose of 600 mg. excreted in a given patient at a given time depends upon the degree of saturation. If the excess intake is stopped, the urinary output falls to normal levels. If the patient is now placed on a vitamin C-free diet, he continues to excrete normal amounts for a time. In other words, the body slowly gives up its store. Eventually, if the patient is continued on a vitamin C-free diet, the urinary output will fall to very low levels until, with depletion of the reserve, the excretion becomes negligible.

Johnson and Zilva[13] gave a somewhat different definition of saturation. They showed that in patients with a previous history of low vitamin C intake there is an initial level below normal in urinary excretion of the vitamin. The response to the test dose is not very great and not until several days of high intake have elasped does excretion begin to rise. And, finally, not until an additional number of days passes, does it attain a constant level. These authors considered a patient saturated when he reached this constant level. The length of time required to reach complete saturation is greater in people with a background of low vitamin C intake than in normal persons on the same dosage.

Youmans and his co-workers[29] have suggested that complete saturation does not indicate a normal degree of vitamin C storage

but rather an artificial state created by excessive intake. It seems fair to assume, however, that the excretion of about 30% of the test dose in a patient indicates an approximately normal state.

Case Report. M. R., a female, aged about 60, was admitted to this hospital on February 16, 1936, complaining of painful bluish areas on the surface of the body, especially the legs, of 10 days' duration. Her family history was non-contributory. She had had her menopause 20 years ago. There had been a previous admission 6 months before with complaints of fever and a generalized eruption. She remained in the hospital for 3 weeks, during which time her symptoms cleared up, and complete roentgenologic, serologic, and bacteriologic studies failed to reveal the nature of her illness. She then remained apparently well until 10 days prior to the present admission when she began to develop painful ecchymotic areas on the knees, thighs and gluteal regions, associated with generalized muscle tenderness. No history of trauma could be elicited. Anorexia appeared. Several days after the onset she had a spontaneous nose bleed of short duration. The next day she developed blueness over one eye. For the week prior to admission there was swelling of the gums with tenderness, but no bleeding. There was no melana, hematuria, or hemoptysis. Further questioning revealed the fact that she lived alone. For the past year her food intake had consisted chiefly of dairy products and soups; she had taken practically no vegetables, fruits, or meats.

FIG. 1.—Subcutaneous hematoma on thigh.

Physical Examination. Temperature, pulse and respirations were normal. She was an elderly woman in no apparent distress other than from pain in the lower extremities. Her mental condition indicated senile changes. The skin was dry, scaly, and atrophic. The lips and nail beds were slightly cyanosed. Numerous small purpuric areas were present on the skin surface. There were a number of large hematomata on both lower extremities, especially the left, where one large patch covered the entire inner and under aspect of the thigh (Fig. 1), and another the inner calf (Fig. 2). A similar lesion was located above the symphysis pubis. These were hard, brawny, and extremely tender. The retinæ were normal. All teeth were absent

except the stumps of the two lower central incisors. The gums were normal, except around these two teeth where they were swollen and hemorrhagic. A small reddish spot was present on the right posterior pharyngeal wall. Examination of the heart, lungs, abdomen, and pelvis was essentially negative. There was no glandular enlargement. A Parkinsonian tremor was present.

Laboratory Data. Red blood cells 2,500,000 per c.mm., hemoglobin 58% (Sahli); white blood cells 3100, neutrophils 66%, unsegmented 2, lymphs. 26, monos 6%; smear showed anisocytosis and slight polychromatophilia; platelets 186,000 per c.mm.; reticulocytes 2.6%; coagulation time 4½ minutes; clot retraction normal; bleeding time 3 minutes. The tourniquet test was markedly positive. The urine was negative. Blood Wassermann test was negative. Blood volume by Rowntree method 4235 cc. (103 cc. per kilo); plasma volume 3078 (75 cc. per kilo). Stools were negative for occult blood. Electrocardiogram was normal. Roentgen-rays of the chest and long bones were normal.

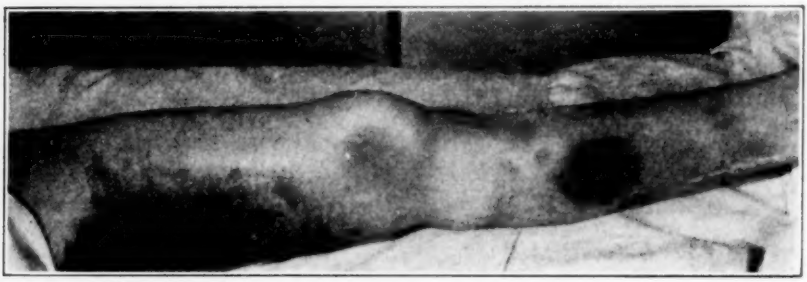

FIG. 2.—Subcutaneous hematoma on thigh and calf.

Course. The laboratory data presented ruled out the primary blood dyscrasias. On the basis of the history and physical findings, together with the negative results of the blood examinations, the diagnosis of scurvy was made. After several days of observation and control studies, she was placed on a régime high in vitamin C content. This consisted partially of orange juice (containing 18 mg. of cevitamic acid per ounce) and partially of cevitamic acid (Hoffman-La Roche) (Chart I). The patient's general condition promptly began to improve; she became brighter, more alert, and interested in her surroundings. There were no fresh hematomata or purpuric spots: The old ones almost immediately began to clear up, and gradually disappeared. The gum lesions also improved considerably. Her red blood count rose to 3,650,000 per c.mm., and hemoglobin to 73%; the leukopenia persisted. The response to tourniquet test gradually diminished until it was only very slightly positive. By the tenth day of treatment she was entirely cured, but remained for 7 additional days of study.

As soon as the diagnosis was established, studies of the urinary output of cevitamic acid were begun. The method of urinary titration used was Birch, Harris and Ray's[5] modification of Tillman's determination. The urine was collected from 8 P.M. to 8 P.M. in dark colored bottles to which 10 cc. of glacial acetic acid had been previously added. The dye (2 to 6 dichlorphenol-indophenol) was standardized every 2 to 3 days against a known amount of

cevitamic acid. The urine was titrated 3 to 4 hours after voiding. Five-hundredths of a gram of dye were dissolved in a small amount of boiling water, and more boiling water up to 25 cc. was added. The resulting solution was filtered. A solution of accurately weighed cevitamic acid was titrated with the dye until the solution turned pink, thus standardizing the dye, 0.05 cc. of which usually equalled about 0.025 mg. of cevitamic acid. For titrating urine, 0.05 cc. of dye were placed in a test tube to which about 2 cc. of water were added. The dye was titrated with urine which was acid to litmus paper, until the red color of the dye changed to the color of the urine, a little of the urine in another test tube being used for comparison. The 24-hour excretion of the vitamin could then be calculated.

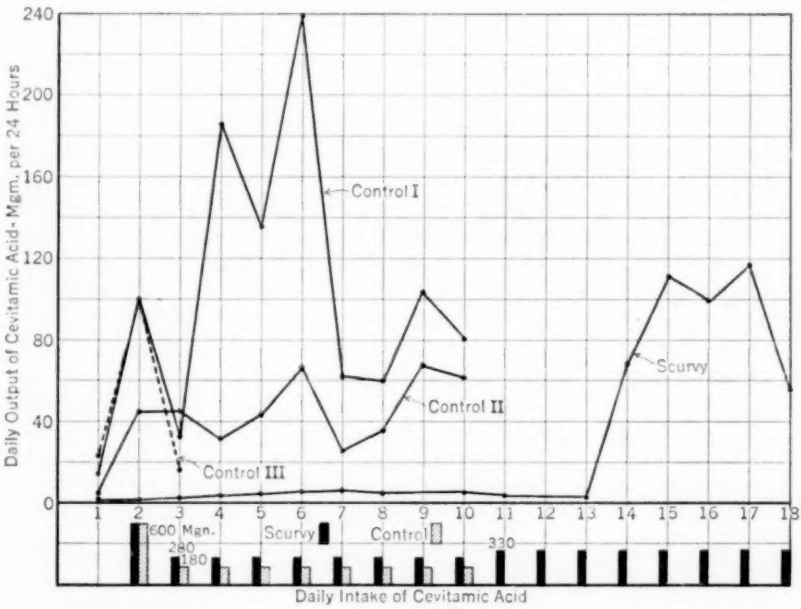

CHART I.—Daily urinary vitamin C excretion of case of scurvy and 3 controls.

The results are tabulated in Chart I. For the first 24 hours, on a control diet, the excretion was 1.75 mg. She then received a test dose of 600 mg. of cevitamic acid, given orally, followed by daily doses of 280 mg. for 8 days, and then 330 mg. for 8 more days. Despite these large doses, the daily excretion for 24 hours remained below 6.5 mg. On the twelfth day, a rise in the curve took place and higher levels of excretion were then maintained. At the time the rise occurred, the patient was symptomatically cured, and insisted upon leaving the hospital a few days later, thus preventing further studies which would have been desirable.

For contrast, the chart shows the output curves in a few controls. Curve I, of a case of pernicious anemia, shows an initial output of 14.4 mg. The test dose of 600 mg. resulted in an excretion of 100 mg. Thereafter, on 180 mg. daily, a high level of excretion was obtained. Curve II, of a case of inactive rheumatic fever, showed lower levels of excretion, but much higher than those of the scurvy patient. The short Curve III shows the response to the test dose of 600 mg. of one of us (A. N.).

Comment. From a diagnostic viewpoint, several features deserve comment. The hematomata were characteristic of scurvy in that they were hard, brawny, and extremely tender; this is known as "scurvy sclerosis".[11,15] The presence of hemorrhages in only those portions of the gums surrounding teeth is extremely characteristic, being stressed by such leading authors on scurvy as Hess,[11] Selle and Rosenberg,[20] Schultzer.[19b] Roentgenologic changes in the bones and joints, while frequently seen in childhood scurvy, are rarely seen in the adult form.

It is well established now, since Schultzer[19a] in 1933 first cured a case of scurvy with intravenous injections of cevitamic acid, that the latter substance alone, given orally or intravenously, is efficacious in curing the disease. This was confirmed by Neumann,[16] Brugsch,[6] Wentzler,[26] Goettsch,[7] Bell,[4] and Svensgaard[21] in infants and recently by Wright and Lillienfeld[28] and Bauke[3] in adults.

Discussion. In reviewing the literature, we have found only 4 cases of adult scurvy where similar studies were made. Wood,[27] in 1935, reported a case in which the initial output was zero, compared to 53 mg. in a control; the output after the test dose of 600 mg. was 1.7 mg. in the scorbutic patient, compared to 231 mg. for the control. On 80 mg. a day, the patient showed clinical improvement, and was discharged after 12 days, during which time there was no vitamin C excretion in the urine.

Since our studies were completed, Schultzer[19b] has reported 3 cases of scurvy in which very complete urinary studies were made. His results differ from ours in that his initial levels were either normal or somewhat subnormal though, in general, they ranged below his controls. Schultzer, himself, remarks that his initial levels are surprisingly high. He gave his patients daily doses of 300 mg. intravenously, 600 mg. intravenously, and 600 mg. orally, respectively. His curves, showing the response to large doses of cevitamic acid, are very similar to ours and show considerable evidence of unsaturation when compared to his controls. The 3 cases required a total of 9.5, 7, and 14.4 gm. of cevitamic acid over a period of 5, 2 and 3 weeks before "saturation" was reached, using the criteria of Johnson and Zilva.[13] In 6 controls, however, similar urinary responses were obtained after 5 to 7 days on 600 mg. daily. In all 3 cases, marked clinical improvement was noticed after 2 to 3 days of high vitamin C therapy.

Harris and Ray[17] found subnormal excretion in two scorbutic children with no appreciable increase in output after the test dose. After cure had been effected, excretion was normal, the test dose then resulting in excretion of a large percentage of the intake.

In our scurvy case there is obvious evidence of tremendous unsaturation, so much so that with an intake of almost 3.7 gm. of cevitamic acid in the first 13 days, she practically excreted none. During this time her tissues were gradually storing the vitamin, so that on the 12th day she excreted about 18% of her intake. In other words, she was now beginning to respond like a normal person. This she continued to do for the remaining 5 days of the study. Control I, however, showed a normal initial level, excreted 100 mg. of the test dose, indicating a normal degree of "saturation," and then continued to excrete a high percentage of the intake. In Control II, however, there was an initial level of 6, with a response of only 45 to the test dose. Excretion following the oral intake of 180 mg. daily was never higher than 67. This curve is lower than that of Control I, although much higher than of our case of scurvy. This patient was a cardiac who had long been on restricted diets. Abbasy, Harris, and Ray,[1] in doing excretion studies on random cases in a large children's hospital, found evidence of considerable unsaturation in many. In reviewing the records they found these to be cases where for one reason or another there had previously been a low vitamin C intake. They used these results to further the concept of subclinical scurvy, first introduced by Hess and Fish[12] in 1914, interest in which has been stimulated in recent years by the advances in the field of vitamin C excretion. This subject is beyond the realm of our paper.

Summary. A case of adult scurvy is presented. The study of the urinary excretion of vitamin C showed evidence of tremendous bodily unsaturation of the vitamin when compared to values obtained by other authors for normal individuals and to our own controls.

We wish to express appreciation to Dr. I. W. Held for his constant interest, and to Dr. H. Schwarz who stimulated our interest in the subject of vitamin C excretion in general.

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FEBRILE ALBUMINURIA.

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The production of artificial fever, in addition to its value in therapy, offers a rather unusual opportunity to study the physiology of the body in the presence of an uncomplicated temperature elevation. Bierman and Fishberg[1] have recently contributed a great deal of our knowledge of this subject. I have been particularly interested in the relation of fever to albumin in the urine, a matter which these authors did not consider, and have had the opportunity to study from this point of view 40 patients receiving fever therapy at this hospital.

The term "febrile albuminuria" was applied by Gerhardt,[4] in 1868, to describe the increase in urinary proteins during elevation of the body temperature, although first mentioned by Martin-Solon[7] some 30 years before. Since Gerhardt's time the term has been used quite extensively, but whether or not fever *per se* actually causes an increase in the amount of urinary protein has not been determined, judging from a survey of the medical literature.

All modern textbooks of medicine call attention to the phenomenon but opinions vary as to the real cause. A. M. Fishberg, for example, says: "Albuminuria may occur in almost any febrile state, but is most common when the fever is very high and protracted . . . . Anatomically, cloudy swelling of the epithelium, particularly of the convoluted tubules, is found. Not uncommonly, there is also fatty change of varying degree, though rarely marked. The albuminuria is generally attributed to these changes in the renal epithelia. It should be mentioned, however, that similar cloudy swelling and fatty change may be found where there was no albuminuria during life. . . . . *It has not been proved that the renal lesions and albuminuria are due directly to the elevation of temperature.* [My italics.] Against such a view is the fact that fever may be very high for a considerable time without accompanying albumin-

uria. Injury to the renal cells by circulating toxic substances would seem more probable, for similar renal lesions and albuminuria occur in various afebrile toxemias and chemical poisons."

Opposed to this Osler and McCrae[8] state: "Pyrexia, by whatever cause produced, may cause slight albuminuria, due to slight changes in the glomeruli induced by fever, such as cloudy swelling which cannot be regarded as an organic lesion. It is extremely common, occurring in pneumonia, diphtheria, typhoid fever, malaria, especially the æstivo-autumnal type, and in acute tonsillitis. The amount is slight, and it usually disappears with the cessation of fever."

The majority of other authors believe with Fishberg that the albuminuria is a manifestation of the accompanying infection and toxemia rather than of the fever itself. The difficulties, of course, have been that fever is almost always caused by an infectious process, and that the probable causative factors have never existed alone. However, in fever therapy one has a marked elevation of body temperature maintained for several hours without an accompanying infection, *a true uncomplicated fever*. Conditions are ideal for the study of febrile albuminuria.

The method of study used was as follows: Patients being treated in this department, who suffered from general paresis, atrophic arthritis, gonorrheal arthritis and chorea, were used. All had a blood-urea nitrogen within normal limits, a normal Mosenthal concentration test and several negative examinations of the urine for albumin. Fever was induced by means of the Kettering hypertherm and an average temperature of 105° to 106° F. was maintained for 4 to 6 hours. A specimen of urine was obtained before the febrile period; a second specimen was collected after fever had reached its height and had been maintained for several hours; the third specimen was the first urine voided after the temperature had fallen to normal, usually 2 to 3 hours after removal from the fever cabinet. These urines were then examined as to specific gravity, reaction to litmus paper, and for gross albumin by the sulphosalicylic acid reagent. The exact amount of urinary albumin was determined by the quantitative sedimentation method of Shevky and Stafford[9] in which the albumin is precipitated by Tsuchiya's reagent, centrifuged in a specially designed tube and the volume of the precipitate read directly on a scale. Results are shown in Table 1.

In 95% of the subjects the pre-fever urine albumin was below 0.03% and 80% presented a figure below 0.02%. The urine albumin exceed 0.04% in only 1 patient. These are normal values and offer better proof of absence of renal disease in the group than the blood-urea nitrogen and the Mosenthal test.

During the febrile period 22.5% of cases showed a decrease in albumin with fever while 77.5% (31 of the 40 patients) had an increase in the level of urine albumin. This increase was very

TABLE 1.—URINE FINDINGS BEFORE, DURING AND AFTER FEVER.

No.	Name.	Sp. gr.	Reaction.	Gross alb.	Quant. alb., per cent.
1	W. M.	b.f. 1.020	Acid	Negative	0.007
		d.f. 1.015	Acid	Negative	0.018
		a.f. 1.008	Acid	Negative	0.007
2	C. S.	b.f. 1.010	Acid	Negative	0.007
		d.f. 1.017	Acid	Cloud	0.081
		a f. 1.020	Acid	Negative	0.014
3	F. S.	b.f. 1.022	Alkaline	Negative	0.017
		d.f. 1.024	Acid	Trace	0.030
		a.f. 1.010	Alkaline	Negative	0.014
4	H. S.	b.f. 1.022	Alkaline	Negative	0.029
		d.f. 1.026	Alkaline	Cloud	0.054
		a.f. 1.022	Alkaline	Cloud	0.075
5	B. W.	b.f. 1.020	Acid	Negative	0.010
		d.f. 1.022	Acid	Trace	0.030
		a.f. 1.018	Acid	Negative	0.015
6	C. E.	b.f. 1.016	Acid	Negative	0.015
		d.f. 1.020	Alkaline	Negative	0.054
		a.f. 1.022	Alkaline	Negative	0.020
7	J. T.	b.f. 1.012	Acid	Negative	0.010
		d.f. 1.012	Acid	Trace	0.054
		a.f. 1.016	Acid	Negative	0.007
8	E. G.	b.f. 1.012	Alkaline	Negative	0.007
		d.f. 1.020	Alkaline	Negative	0.010
		a.f. 1.020	Acid	Negative	0.020
9	C. N.	b.f. 1.018	Alkaline	Negative	0.010
		d.f. 1.025	Alkaline	Negative	0.016
		a.f. 1.010	Alkaline	Negative	0.007
10	M. C.	b.f. 1.022	Alkaline	Negative	0.002
		d.f. 1.022	Alkaline	Negative	0.003
		a.f. 1.010	Acid	Negative	0.018
11	M. J.	b.f. 1.020	Acid	Negative	0.014
		d.f. 1.020	Alkaline	Cloud	0.065
		a.f. 1.030	Acid	Cloud	0.097
12	J. B.	b.f. 1.017	Alkaline	Negative	0.018
		d.f. 1.022	Alkaline	Negative	0.072
		a.f. 1.025	Alkaline	Negative	0.065
13	A. H.	b.f. 1.024	Acid	Negative	0.017
		d.f. 1.036	Alkaline	Negative	0.014
		a.f. 1.036	Acid	Negative	0.049
14	C. J.	b.f. 1.020	Acid	Negative	0.007
		d.f. 1.026	Acid	Negative	0.004
		a.f. 1.026	Acid	Negative	0.005
15	T. D	b.f. 1.030	Acid	Negative	0.072
		d.f. 1.030	Acid	Negative	0.076
		a.f. 1.025	Alkaline	Negative	0.014
16	A. D.	b f. 1.020	Acid	Negative	0.025
		d.f. 1.018	Alkaline	Negative	0.018
		a.f. 1.022	Alkaline	Negative	0.025
17	A. G.	b.f. 1.022	Acid	Negative	0.007
		d.f. 1.032	Alkaline	Negative	0.022
		a.f. 1.010	Acid	Negative	0.000
18	R. K.	b.f. 1.020	Acid	Negative	0.022
		d.f. 1.022	Acid	Negative	0.018
		a.f. 1.015	Acid	Negative	0.018
19	G. C.	b.f. 1.022	Acid	Negative	0.024
		d.f. 1.030	Acid	Negative	0.040
		a.f. 1.010	Acid	Negative	0.007
20	A. K.	b.f. 1.032	Acid	Negative	0.022
		d.f. 1.030	Alkaline	Negative	0.025
		a.f. 1.032	Alkaline	Negative	0.036
21	R. A.	b.f. 1.030	Acid	Negative	0.011
		d.f. 1.032	Acid	Negative	0.018
		a.f. 1.022	Acid	Negative	0.014
22	F. P.	b.f. 1.010	Acid	Negative	0.011
		d.f. 1.016	Acid	Cloud	0.061
		a.f. 1.025	Acid	Cloud	0.086
23	C. D.	b.f. 1.030	Acid	Negative	0.007
		d.f. 1.025	Acid	Negative	0.011
		a.f. 1.040	Acid	Negative	0.022
24	W. C.	b.f. 1.012	Acid	Negative	0.004
		d.f. 1.022	Acid	Negative	0.022
		a.f. 1.016	Acid	Negative	0.011
25	E. S.	b.f. 1.018	Acid	Negative	0.007
		d.f. 1.018	Alkaline	Negative	0.032
		a.f. 1.015	Acid	Negative	0.025
26	R. S.	b.f. 1.025	Acid	Negative	0.025
		d.f. 1.032	Acid	Negative	0.007
		a.f. 1.022	Acid	Negative	0.001
27	E. F.	b.f. 1.020	Acid	Negative	0.011
		d.f. 1.020	Alkaline	Negative	0.007
		a.f. 1.020	Alkaline	Trace	0.022

TABLE 1.—URINE FINDINGS BEFORE, DURING AND AFTER FEVER.—(*Continued.*)

No.	Name.	Sp. gr.	Reaction.	Gross alb.	Quant. alb., per cent.
28	M. H.	b.f. 1.022	Alkaline	Negative	0.004
		d.f. 1.025	Acid	Negative	0.036
		a.f. 1.025	Acid	Trace	0.040
29	A. R.	b.f. 1.018	Acid	Negative	0.004
		d.f. 1.024	Acid	Negative	0.011
		a.f. 1.030	Acid	Negative	0.025
30	E. H.	b.f. 1.012	Acid	Negative	0.007
		d.f. 1.025	Acid	Cloud	0.374
		a.f. 1.028	Acid	Negative	0.032
31	M. H.	b.f. 1.025	Alkaline	Negative	0.014
		d.f. 1.032	Alkaline	Trace	0.043
		a.f. 1.010	Alkaline	Negative	0.018
32	E. W.	b.f. 1.010	Acid	Negative	0.004
		d.f. 1.018	Acid	Negative	0.007
		a.f. 1.018	Acid	Negative	0.007
33	R. L.	b.f. 1.020	Acid	Negative	0.007
		d.f. 1.030	Alkaline	Negative	0.005
		a.f. 1.025	Acid	Negative	0.011
34	A. B.	b.f. 1.025	Alkaline	Negative	0.036
		d.f. 1.020	Alkaline	Negative	0.022
		a.f 1.030	Acid	Cloud	0.115
35	R. W.	b.f. 1.020	Alkaline	Negative	0.020
		d.f. 1.030	Acid	Negative	0.220
		a.f. 1.020	Acid	Negative	0.020
36	T. N.	b.f. 1.012	Acid	Negative	0.004
		d.f. 1.018	Acid	Trace	0.022
		a.f. 1.014	Acid	Negative	0.014
37	C. E.	b.f. 1.018	Acid	Negative	0.010
		d.f. 1.020	Alkaline	Trace	0.032
		a.f. 1.020	Acid	Negative	0.011
38	E. M.	b.f. 1.022	Alkaline	Negative	0.011
		d.f. 1.020	Alkaline	Negative	0.032
		a.f. 1.018	Alkaline	Negative	0.018
39	B. A.	b.f. 1.015	Alkaline	Negative	0.009
		d.f. 1.010	Alkaline	Negative	0.006
		a.f. 1.015	Acid	Negative	0.018
40	M. W.	b.f. 1.015	Acid	Negative	0.014
		d.f. 1.020	Acid	Negative	0.060
		a.f. 1.008	Acid	Negative	0.025

b.f. = before fever. d.f. = during fever. a.f. = after fever.

definite, being more than 100% in 20 of the subjects and over 200% in 16 cases. On 4 occasions the albumin level increased 500%. The complete tabulated results are:

Decrease.		*Increase.*	
No. of cases.	Per cent.	No. of cases.	Per cent.
2	0 to 50	4	0 to 50
7	50 to 100	7	51 to 100
—		4	101 to 200
9		5	201 to 300
		3	301 to 400
		4	401 to 500
		4	Over 500
		—	
		31	

This seems to prove conclusively that fever alone in the majority of cases provokes a rise in the amount of urine albumin. Frequently double or triple the normal level is reached.

It should be emphasized, however, that in spite of the rather large percentage rise, the actual albuminuria is not likely to be massive. During fever only 9 of the 40 cases showed albumin in the urine as determined by the sulphosalicylic acid method. One must remember, however, that the patients had a temperature

elevation for only a few hours. Had this been maintained for days, as is the rule in infectious fevers, it is probable that larger amounts would have appeared.

The relationship of the specific gravity to elevation of the temperature is shown in Table 1. While some increase in the specific gravity usually occurred during fever, this was never very great. Actually in 32.5% (13 subjects) the specific gravity remained at the pre-fever level or was decreased; in 8 of these there was a rise of the urine albumin. This fact indicates that the patients were not dehydrated (they ingested large amounts of normal saline solution during the treatment and did not lose weight). It follows, then, that *the increase in albumin was not relative* and due to dehydration with consequent increase in urinary concentration, but actually represented increased excretion due to fever.

Comparison of the pre-fever and post-fever urine albumin levels indicated that 70% of the subjects continued to show an increase in albumin in the specimens voided following return of the temperature to normal. This suggests that the increased output is carried over into the post-fever stage; the possible delay in voiding, however, must be considered in evaluating these results.

From those studied, the mechanism of the occurrence of albumin in the urine of febrile patients is not apparent. One can only say that it does occur and that it is not altogether a manifestation of existing toxemia and infection. A tenable explanation is that of cutaneous vasodilatation. This might produce a relative anoxemia of the kidneys with consequent increased membrane permeability. The possibility that the fever may have itself temporarily damaged the renal epithelium with temporarily increased permeability must also be considered.

Summary. 1. Forty patients have been studied from the standpoint of urinary albumin level before, during and after an uncomplicated fever.

2. True febrile albuminuria of varying degree occurs in over 75% of cases. This increased level is carried over into the post-fever stage.

3. The mechanism may be that of relative renal anoxemia following cutaneous vasodilatation.

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HUMAN AUTONOMIC PHARMACOLOGY VI. GENERAL AND LOCAL SWEATING PRODUCED BY ACETYL-BETA-METHYL-CHOLINE CHLORIDE (MECHOLYL).*

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One of the most prominent and spectacular responses of the autonomic nervous system to acetyl-beta-methylcholine chloride (mecholyl) is the drenching perspiration.[9] This effect of the drug occurs within a few minutes following a subcutaneous injection of sufficient dosage and is part of a general pouring out of secretions and excretions, including those from the mucous membranes of the eyes, nose, mouth, throat, and stomach. Generally speaking, from 15 to 30 mg. subcutaneously of mecholyl will cause, in the average patient, a marked perspiration together with the systemic effects which have been described in the literature.

A general discussion of the sweating mechanism with references to a considerable part of the literature is given by Yas Kuno.[5] He records the relationship between pilocarpine and atropine and discusses the theories of the sweat mechanism. Many early workers observed the alkalinity of the sweat, although references to this phenomenon seem to have disappeared from the literature. In 1852, Favre[2] observed that the sweat may pass over from acid to alkaline reaction. In the same year, a French writer, Gillibert d'Hercourt,[3] noted the transition of the sweat from acidity to neutrality. In 1874, Robin[11] demonstrated this phenomenon. Heuss,[4] studying the reaction to pilocarpine, definitely demonstrates this change of reaction. This is likewise noted by Camerer,[1] in 1902. Minor,[7] in 1928, made possible the photography of sweat by his iodine paste technique.

The patients used in the following experiments were the same group we have used in our previously recorded experiments, namely, patients suffering from dementia præcox who are otherwise healthy and who present no marked vasomotor disturbance. Whatever

* Aided by grants from the Commonwealth of Massachusetts, the Rockefeller Foundation and the Herbert L. Celler Foundation.

control experiments we have done on normal individuals show that these patients, so far as sweating reactions are concerned, may be considered normal.

We record here certain phenomena not hitherto described in the literature which are of importance in respect to the physiology of the sweat mechanism.

1. *The Alkalinity of the Mecholyl Sweating Reaction.* It is currently and commonly stated in the literature that sweat is acid. This is true if the usual technique is followed; that is, if a piece of litmus paper is rubbed over a sweating zone and rubbed against the skin. In 1878, Trümpy and Luchsinger[12] noted that sweat produced by pilocarpine was alkaline. Furthermore, these authors noted that the production of sweat under pilocarpine on a previously washed side of the face was immediately alkaline as compared with the sweat on the unwashed side of the face which was acid, and which later also became alkaline. Metzner,[6] carrying the observations of these authors further, explained that the acid reaction of sweat was due to fatty acids normally present in the skin, and that if these were removed, sweat usually was somewhat alkaline.

The sweat produced by mecholyl is always alkaline if care is taken to test the sweat droplet and not rub the litmus paper against the skin. Furthermore, if the skin is previously thoroughly cleansed by soap, water, alcohol, and ether, the sweat is universally alkaline following any technique used; that is, immediately following the mecholyl injection the sweat becomes definitely and decidedly alkaline.

pH determinations made in two subjects showed that following subcutaneous injection of 25 mg. of mecholyl, the pH changed from 6.1 to 8.1 in 1 case, and from 7.5 to 8.5 in the other. This increase in alkalinity is in harmony with results which we record elsewhere;[8] namely, that mecholyl changes the acid secretion of the stomach to alkaline, and is in line with observations made more roughly which indicate that the tears, nasal secretion and saliva are rendered more alkaline by this chemical. In other words, the increased alkalinity of the sweat is part of a general reaction of the excretions and secretions of the body.

2. *Effect of Atropine on the Mecholyl Sweat.* Atropine, given in advance of the mecholyl injection in dosage from 1/100 to 1/50 gr. prevents the sweating reaction, just as it prevents all other mecholyl responses. Atropine, given at the height of the sweating reaction, stops the sweating within a few months of the injection.

3. *The Synergic Effect of Prostigmin.* It has been shown by many workers that physostigmin and prostigmin are synergic in relationship to the effects of mecholyl and acetylcholine derivatives in general.[10] We have shown this to be true in the case of the gastric secretions in man; that is, a small dose of mecholyl will produce no changes of substantial nature in the gastric secretion, but if a preliminary

treatment with prostigmin or physostigmin is given, the same dose of mecholyl will produce marked changes in gastric secretion.

This is also true of the sweat reaction: 10 mg. of mecholyl injected subcutaneously will, in the average patient weighing about 125 to 150 pounds, produce slight, if any, sweating. If, preceding this injection, the same patient receives 1 cc. of 1 to 2000 prostigmin or $\frac{1}{8}$ gr. of physostigmin, the sweating reaction becomes marked and definitely alkaline.

4. *The Intradermal Sweat Reaction of Mecholyl.* *A.* It was observed by us that following a subcutaneous injection of mecholyl for the purposes of producing the general reaction, there was more sweating around the site of the injection than elsewhere. We consequently carried out a series of experiments on the effect of intradermal injections of dilute solutions of mecholyl. An intradermal injection of 0.1 to 0.2 cc. of 1 to 1000 mecholyl solution will, in the great majority of individuals tested, produce a wheal, then a gradual flushing on the periphery of the wheal, which gradually includes the wheal.* This is followed by a slow elevation of the sweat glandules and then glistening drops of sweat appear at the apex of each gland. Finally, the whole wheal becomes covered with either a thin layer of sweat or is profusely drenched, according to the sensitivity of the individual and the general environmental conditions, such as the heat of the day. This sweat is immediately alkaline, and especially so if the droplets are carefully tested without contact with the skin, and quite universally so if the skin has previously been treated as indicated in the preceding part of this paper.

This local sweating, as we have named it, is very variable in the dosage required to bring it about. In one of our subjects, a member of the research staff, 0.2 cc. of a 1 to 1,000,000 solution was sufficient to effect it. We are of the impression that the sweating reaction decreases in old age, although this has not been studied sufficiently to be established.

B. Control studies with salt solution, adrenalin, benzedrine and distilled water produced no local sweating reaction.

C. The effect of a general sensitization by prostigmin or physostigmin. When 1 cc. of 1 to 2000 prostigmin was given by subcutaneous injection, the sweating observed became increased, and in cases where the dilution of mecholyl was so great as to be without any result in sweating, sweat appeared following the prostigmin injection.

D. If 0.1 cc. of 1 to 2000 prostigmin is mixed with 1 to 1000 mecholyl in equal parts and the combination injected intradermally,

* The seasonal relationship of sweating comes out very importantly in our later experiments. The general sweating reaction is not nearly so profuse in the fall as it is in the summer. The intradermal sweating test at the time of this writing (November) requires a concentration of 1:200 to bring about a good sweating response in those patients in whom 1:1000 was sufficient 3 months ago.

the result in sweating is always greater than when 0.2 cc. of 1 to 1000 mecholyl is given intradermally at the same time and on the opposite side of the chest wall.

E. A very dilute solution of atropine injected into one side of the wheal stops the local sweating.

F. Adrenalin injected into one side of the mecholyl wheal stops the sweating wherever it produces a marked vasoconstriction. Where there is no vasoconstriction, the mecholyl sweating proceeds as before. Benzedrine, on the other hand, given intradermally has no effect upon the local sweating.

5. *The Effect of Iontophoresis on the Sweat Reaction.* Iontophoresis was carried on in the usual way; that is, the negative electrode was moistened with salt solution, and the positive electrode moistened with 1 to 1000 mecholyl solution. After the application of 4 milliampères of current for a period of 5 minutes, the electrodes were removed and the skin reaction watched. Within a few minutes the same reaction appeared as followed the intradermal reaction; namely, flushing, elevation of the sweat glands, and the appearance of glistening drops of sweat, which sweat was alkaline. In other words, the galvanic current had introduced the mecholyl into the skin and an intradermal reaction was produced, differing in no way from the direct intradermal injection.

Summary. 1. The human organism is very sensitive to acetyl-beta-methylcholine chloride (mecholyl) and especially the sweat mechanism.

2. Sweat produced by mecholyl is alkaline, and the alkalinity increases as the reaction goes on.

3. The general sweating reaction can be inhibited by atropine as completely as all the other cholinergic effects of mecholyl.

4. On the other hand, the sweating is enhanced by the drugs synergic to mecholyl, that is, prostigmin and physostigmin.

5. An interesting intradermal local sweating response is here described. This intradermal response is abolished by atropine, and in small doses atropine acts on the local mechanism to prevent the appearance of sweating. Adrenalin inhibits this local intradermal response only by virtue of its vasoconstriction action, since the reaction persists where vasoconstriction does not appear. Sodium chloride and benzedrine were observed to have no effect on the local sweating response.

6. The local sweating response differs in various individuals and may be a criterion of the sensitivity of the individual to parasympathetic or cholinergic stimulation.

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THE CLINICAL EFFECTIVENESS OF LACTIC ACID JELLY AS A CONTRACEPTIVE.

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In spite of its great importance to both this generation and the next, contraception in its medical and physiologic aspects has been given relatively little attention by scientific investigators. This has been due in part to the "taboo" which, to a steadily diminishing degree, custom has imposed on the discussion of matters relating to sex; in part, to the unfounded classification of contraceptives with "obscene matter" in various laws; and, in part, to the conservatism of the boards of trustees under whom research work is carried on. An outstanding example of this conservatism is furnished by the American Medical Association, which, in spite of the medical character of contraceptives and of their widespread use by its members, does not yet permit its Council on Pharmacy and Chemistry to report on their ingredients or on their safety or effectiveness. For these reasons a careful evaluation of contraceptives would appear worth while.

The experience of the birth control clinics has demonstrated the necessity for research into simpler and more generally acceptable methods of contraception than those now used by the clinics. It has become evident that high percentages of success with the diaphragm and jelly method have been achieved by patients using the method carefully. At the same time it has been found that only about half of the patients of many birth control clinics are willing to follow the method with care.

Conscious of an obligation to their patients, the physicians of

birth control clinics have been unwilling to experiment widely with alternative techniques in the hope of finding more acceptable methods of adequate reliability. Exploiting commercial interests, however, have not hesitated to develop a market for some of the materials which appear to be simpler in use and perhaps less expensive than the jelly and diaphragm combination. Of these, jelly used alone especially warrants a careful statistical study at the present time.

Dr. Irving Stein (personal communication) distributed tubes of jelly, each provided with a nozzle, to underprivileged patients. The proper procedure was carefully explained in each case by a social worker who also made repeated visits to the home in order to encourage persistence in the method. Interruption of supplies of jelly made continuous records difficult. Calculating from the time the supplies were first given to the date of the last follow-up in each case, Dr. Stein finds that 112 patients had 44 person-years of exposure to the risk of pregnancy with no pregnancies. Six other patients also had no pregnancies, but the duration of the periods of their exposure is not known. Dr. Stein states that pregnancies occurred after it became necessary to discontinue the social worker. These may have been due in part to the lack of her periodic encouragement.

The jelly used in that experiment was prepared from the following formula:

	Weight %.
Boric acid	2.58
Lactic acid	2.00
Glycerine	9.57
Powdered tragacanth	2.39
Water	83.46

Recent samples have been found to have a pH of about 2.

More recently, Mr. A. R. Kaufman, of Kitchener, Ontario, Canada (personal communication) has distributed contraceptive jelly to over 35,000 cases. A follow-up was made of 1000 of these by comparing the names of the recipients with those in the official birth records of 3 cities. It was found that after 18 months children had been born to 20% of those receiving supplies. It is impossible to convert these figures into pregnancies per hundred years of use of jelly since approximately one-third of the original thousand received condoms with the jelly and nozzle. The pregnancy rate for the combination would appear to lie between 13 and 26 per 1000 person-years of use. That only a small number of these pregnancies occurred while the method was being properly employed is suggested by the reasons given by the users for the failures. These were:

Reason.	Per cent of failures.
Failure to renew supplies	41
Irregular use	47
Condom broke	3
Failure of jelly	9

The jelly employed was said to consist of 1% of lactic acid and 4% of boric acid in a base of glycerite of starch. In the process of manufacture the boric acid was converted into boroglyceride.

Another brief series is available as a result of work done in a mountain community in West Virginia. Jelly was distributed in jars and each patient was given a bulb and syringe applicator which delivered into the vagina a dose of approximately 6 cc. Forty-three cases show a total exposure to pregnancy of 308 months, or roughly 26 years, with 11 undesired pregnancies, or 43 pregnancies per 100 person-years of exposure to the risk of pregnancy. Of these 11 pregnancies, 7 resulted from failure to follow directions carefully. When allowance is made for this fact, 36 patients are found to have had an exposure of 19 years with 4 pregnancies, or 21 pregnancies per 100 person-years of exposure. The qualitative formula as given by the manufacturer is as follows: lactic acid, quinine bi-sulphate, zinc sulpho-carbolate, oxyquinoline sulphate, resorcinol, glycerine, and gum tragacanth. The examination of one sample revealed a pH of 2.9.

In the obstetrical department of the Episcopal Hospital in Philadelphia, located in a manufacturing district, tubes of jelly provided with nozzles were offered to each post-natal case approximately 1 month after delivery. Each patient was informed that the method did not give perfect protection and that she would be given the address of a diaphragm clinic in the neighborhood should she prefer. A charge of $0.20 was made for each tube of jelly and $0.10 for each nozzle. To those purchasing jelly, careful instructions were given for its use. The patients were advised that additional security would result from the simultaneous use of a condom and by avoidance of the more fertile period of the menstrual cycle.

The jelly used was said by the manufacturer to contain 2% lactic acid and 0.025% oxyquinoline sulphate in a vegetable gum base. Recently secured samples were found to have a pH of 2.9.

An attempt was made 26 months after the series was begun, to follow up all the cases more than 6 months old. Of 130 cases it was possible to locate and interview only 83. It is apparent that the selection of cases was not random, but on the basis of proven fertility and sufficient interest in contraception to purchase a tube of jelly and a nozzle for 30 cents.

The 83 patients divided into 3 groups: Group I, those who were regular and careful users; Group II, those who used the jelly irregularly or who discontinued its use; and Group III, those who never used the jelly. Table 1 presents the data essential for a calculation of the pregnancy rates of these three groups during the period in which the jelly was supposed to have been used, together with the same information for those 12 women who became pregnant during this period.

TABLE 1.—PREGNANCY RATES AMONG USERS AND NON-USERS OF JELLY.

Extent of use.	No. of cases.	Per cent of all cases.	Exposure to pregnancy in years.		No. of pregnancies.		Pregnancies per 100 person-years exposure to risk of pregnancy.	
			Undesired.	All.	Undesired.	All.	Undesired.	All.
(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
Group I . .	19	23	26	26	1	1	4	4
Group II . .	42	56	56	57	5	6	9	11
Group III . .	22	26	22	23	4	6	18	26
Total . .	83	100	104	106	10	13	10	12
Those who became pregnant	12	14	9 1	10 7	10	13	110	121

It seems probable that the pregnancy rates of Table 1 are somewhat lowered by the fact that all the cases here reported are postnatal, and that no allowances have been made for this characteristic. The interval between parturition and purchase of the jelly is similar for all groups, however, so that this factor cannot account for the observed differences in the pregnancy rates.

What is essential, of course, in the evaluation of the effectiveness of any contraceptive method is an estimate of the number of pregnancies which would have occurred had not the particular contraceptive method been used. No highly accurate estimate can be made here, but it is useful to compare the pregnancy rates for all pregnancies in the period of using the jelly with the rates for all pregnancies before the jelly was purchased (Table 2).

TABLE 2.—COMPARISON OF PREGNANCY RATES BEFORE AND AFTER PURCHASE OF THE JELLY.

Extent of use (1)	Exposure before purchase in years. (2)	No. of pregnancies before purchase. (3)	Pregnancies per 100 person-years exposure to risk of pregnancy.		
			Before purchase. (4)	After purchase.	
				Undesired. (5)	All (6)
I	72	57	79	4	4
II	162	114	70	9	11
III	89	53	60	18	26
Total	323	224	69	10	12
Those who became pregnant . .	27	31	115	110	121

The method for calculating pregnancy rates has been adapted from Pearl[1] and from Stix and Notestein.[2] From the gross period of exposure the following deductions have been made for infertility:

10 months for each full term pregnancy terminating in live issue; 9 months for each stillbirth; 3 months for each abortion or miscarriage. Those who became pregnant after purchasing the jelly are shown to have had a previous fertility considerably higher than that of the entire series. The differences in fertility before purchasing the jelly are not significant for Groups I, II, and III. Hence the differences among Groups I, II, and III in respect to pregnancy rates while using the jelly cannot be explained in terms of previously demonstrated fertility.

No significant differences were found among the three groups as to educational attainment, age at the time of purchasing the jelly, number of pregnancies at the time of purchasing the jelly, length of marriage at this time, interval between parturition and purchase of jelly, or length of exposure to pregnancy after purchase of jelly. As 43, or more than 50% of all the cases, used on an unspecified number of occasions some method of contraception other than jelly alone, the latter cannot be considered entirely responsible for the reductions in fertility. The extent to which the use of methods alternative or supplementary to jelly alone depressed the observed rates cannot be determined in this preliminary report. The effect of supplementary methods is obvious in Group III, in which 3 were separated from their husbands or employed abstinence, 8 used the condom, and 1 resorted to coitus interruptus. The 9 contraceptive users had a total exposure of 13.4 years with no pregnancies. The 10 remaining in Group III, and stating they had used no contraceptive method, had a net exposure of 9.8 years with 6 pregnancies, making a pregnancy rate of 61 per 100 person-years of exposure to the risk of pregnancy. Although they may account for part of the difference between the rates for Groups II and III, however, differences in the degree of resort to alternative or supplementary methods do not explain the observed differences in the pregnancy rates of Groups I and II. In Group I only 4 admitted the use of methods supplementary to the jelly; 3 employed the condom and 1 the condom and douche, to an unknown extent, without ceasing the regular use of the jelly. In Group II, 30 admitted the occasional use of alternative, supplementary, or substitute methods; 13 relied on the condom, 10 on the condom and douche, 6 on the douche, and 1 on a different jelly. No case in any group stated that the "safe period" method had been used.

Average frequency of coitus was examined and certain differences obtained. For Group I the mean frequency per week was 1.41; for Group II it was 1.73; for Group III it was 1.79; and for those 12 who became pregnant the mean was 1.93. These differences, however, do not appear to be large enough to account for the differences in pregnancy rates.

In following up these 83 cases, care was taken to obtain the

alleged reasons for not using the jelly regularly and carefully. Table 3 presents the frequencies with which the various reasons were given.

TABLE 3.—REASONS GIVEN FOR NOT USING JELLY REGULARLY AND CAREFULLY.

Reason.	Number.	Per cent.
1. Carelessness or negligence	17	26
2. Lack of confidence*	13	20
3. Difficulties in obtaining	7	11
4. Esthetic objections	7	10
5. No reason	5	8
6. Preferred another method	5	7
7. Health objections	3	5
8. Pregnancy desired	3	5
9. No coitus	3	4
10. Religion	2	3
11. Menstruation not resumed	1	2
Total	66	101

* The number of cases in this group was probably increased by the physician's recommendation of the condom and the "safe period" as methods supplementary to the use of the jelly.

Conclusions. 1. An acid contraceptive jelly used both alone and with occasional supplements, gave reasonable protection against undesired pregnancy.

2. A group of 19 patients who used jelly regularly, 4 of whom admitted the use of supplementary methods, and whose total exposure was 26 years, had undesired pregnancies at the rate of 4 per 100 person-years of exposure to the risk of pregnancy.

3. Of 42 others using the method intermittently, 30 relied in part on other methods. The total exposure was 56 years, and the rate for undesired pregnancies was 9 per 100 person-years.

4. A comparable group of 22 patients in the series did not use the jelly they purchased but half of them employed other contraceptive methods, reducing the rate for undesired pregnancies to 18 per 100 person-years of exposure.

5. The average pregnancy rate for all pregnancies in the entire series of 83 patients before the purchase of the jelly was 69 per 100 person-years of exposure.

6. Of 83 patients who purchased contraceptive jelly 1 month after delivery, 23% used the jelly faithfully, 51% intermittently, and 26% never used it. The acceptability of the jelly, modified by the conditions of its prescription, appears low.

Since this article went to press, Dr. Hannah Stone[3] has reported an excellent clinical study of contraceptive jellies. The data given do not permit a direct comparison of the results with those here reported.

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DIABETES AND PREGNANCY.

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Since the introduction of insulin, an increasing number of diabetics have become pregnant due to prolongation of the lives of juvenile diabetics and the increased fertility of adult diabetics. In the future, we must expect the occurrence of pregnancy in diabetes to engage with increasing frequency the attention of both the internist and the obstetrician. This paper deals with maternal mortality in diabetics, the fetal death rate, diagnosis, and the medical and obstetrical care of such women.

Maternal Mortality. In 118 cases collected by Skipper[8] there was a maternal mortality rate of 9.3%, although none of his own 33 cases died. Williams[11] found, in 1909, a death rate of 27%. In the 51 diabetics delivered at the Boston Lying-in Hospital since 1916 there were no deaths from diabetes, the sole fatality being in a woman who had severe eclampsia. We may assume, therefore, that the outlook is good for a diabetic woman contemplating pregnancy.

Fetal Mortality. Skipper found a gross fetal mortality of 45.2% in his collected cases, which is no improvement over the 41% reported by Williams before the days of insulin. In Skipper's own 33 hospital cases there was a fetal death rate of 40%. In his last 13 cases, treated with special care, 3 babies died, a mortality of 23%.

At this hospital between 1916 and 1932 there were 34 diabetic pregnancies which were productive of 35 infants, since there was one pair of twins. Of these, 15 were non-viable, stillborn, or died after birth, giving a gross fetal mortality of 42.8%. Of more importance from the standpoint of the hospital is the death rate among infants that had a fair prospect of survival when their mothers first presented themselves at the clinic. If the fetus is alive *in utero* when the patient first applies for treatment, if it is not malformed or under 4 pounds when delivered, we believe that such an infant should have a good prognosis for life. A stillbirth or neonatal death occurring in this group is a net fetal mortality. Of the 35 infants, 28 belonged in this category, and 7 of them died, a net mortality of only 25%.

Since 1932, the care of all diabetics has been under the supervision of the authors of this report. There have been 18 diabetic pregnancies. One of the patients was first seen in coma with a dead

fetus undelivered. Two other infants were stillborn or died after birth, giving a gross fetal mortality of 16.7%. There were 17 cases in which a living infant might have been expected, with two deaths, a net fetal mortality of 11.7%. It is therefore apparent, so far as one may draw conclusions from a small number of cases, that both the gross and the net fetal mortality have been decreased by half. The two stillbirths occurred in Cases 3 and 12. In Case 3 the baby died early in the last month. Unfortunately, a postmortem examination could not be obtained. In Case 12 the baby died 4½ weeks before term. This baby, while it appeared normal externally, showed a large heart with glycogen infiltration of the myocardium at postmortem. A Cesarean done 2 weeks from term could not have saved either baby.

It would seem that there are three factors involved in the high fetal mortality of diabetes. These are: 1, neglect of the disease, either by the patient or by the physician, resulting in acidosis; 2, excessive size of the fetus; and 3, an increased frequency of fetal anomalies. From our own experience, as well as from a study of the literature, the most frequent cause of fetal death is neglect of the diabetes with resultant acidosis. Four of our 18 infants weighed 10 pounds or more, and the average weight was 8 pounds, 11 ounces, so that these babies appear to be larger than normal. Three per cent of the infants in Skipper's collected cases had congenital abnormalities. Three of the 53 infants in this hospital's cases (5.7%) presented malformations inconsistent with life. Of less importance are fetal hyperglycemia and congenital diabetes. Hydramnios is less frequent since the introduction of insulin.

Diagnosis. Lactosuria may occur in the latter months of pregnancy and be confused with diabetes. Non-diabetic glycosuria is more frequent in the pregnant than in the non-pregnant. It is usually ascribed to lowering of the renal threshold, but there is also a slightly impaired carbohydrate utilization, producing a high initial alimentary hyperglycemia, as is demonstrated by the following example:

Before delivery.			*After delivery.*		
Hours.	Blood sugar.	Urine.	Hours.	Blood sugar.	Urine.
0	102	..	0	88	Green
½	178	0	½	146	Green
1½	202	Yellow brown	1½	138	Green
3	91	Yellow brown	3	90	Green

The fermentation test distinguishes glucose from lactose. In all cases where sugar is found in the urine we perform blood sugar tests 2 hours after meals or glucose tolerance tests. With lactosuria there should be no marked elevation of the blood sugar. We have made the diagnosis of diabetes only if the fasting blood sugar is 120 mg.% or more, or if the blood sugar 3 hours after the ingestion of 100 gm. of glucose is 120 mg.% or more. Several patients presented high

intermediate curves, but since the blood sugar was not elevated at the end of 3 hours we did not consider them diabetics, although they were carefully observed subsequently. None of them experienced any difficulty at delivery or in the puerperium, nor did they develop positive evidence of diabetes. One of our patients (Case 10) was first seen when 7 months pregnant with the following sugar tolerance tests.

Before delivery.			*7 weeks after delivery.*		
Hours.	Blood sugar.	Urine.	Hours.	Blood sugar.	Urine.
0	143	Brown	0	116	0
½	222	Red	½	167	Trace
2	153	Brown	2	83	Trace
3	125	Yellow			
A diabetic curve.			A non-diabetic curve.		

Another curve determined a year postpartum was also non-diabetic, indicating that the patient had suffered from mild diabetes according to our standards, which improved after pregnancy. Two other patients (Cases 17 and 18) behaved in a similar fashion. They were both fat women. There was also one patient with known renal glycosuria. There is still a great deal to be learned about carbohydrate metabolism in normal pregnancy. It is possible that our standards are too low although they are the most stringent in the literature.

Management of Diabetes During Pregnancy. Once the diagnosis is made the patient is usually admitted to the hospital a few days for regulation and instruction. She is given a diet of 150 gm. of carbohydrate, 70 to 80 gm. of protein and fat according to the state of her nutrition. One quart of milk a day is included and she is given cod-liver oil or viosterol. Pre-meal specimens of the urine are examined. If the glycosuria continues, insulin is administered until it is controlled. On several occasions we were surprised to find that the patient needed more insulin than we had expected from the degree of glycosuria. If the gravida is in the last month of pregnancy, stereoroentgenometric measurements of the fetus are made according to the method of Johnson.[4] She is sent home with instructions to test her urine before each meal and at bedtime until we are sure that there is no sudden shift in tolerance. She is then seen at weekly intervals.

It is generally believed that there is a definite improvement in diabetes during pregnancy because of the increased insulin supply produced by the fetal pancreas. This view is supported by the work of Carlson and Drennan,[1] and of Carlson and Ginsburg,[2] who found that the diabetes produced by pancreatectomy in pregnant bitches was far less severe than that in the non-pregnant. This work was repeated by Markowitz and Soskin[5] who found, on the contrary, that pancreatectomy in pregnant dogs resulted in diabetes of the same severity as that in the normal controls. Further, they found

Summary of Findings in Authors' Cases of Diabetes and Pregnancy, 1932–1936.

Name.	Para.	Age.	Family history of diabetes.	Obstetrical history.	Onset of diabetes.	Insulin before pregnancy.	Insulin during pregnancy.						Insulin after delivery.	Method of delivery.	Condition of baby.*	Lactation.	Complications.	Remarks.
							0–4 m.	5 m.	6 m.	7 m.	8 m.	9 m.						
1. C. W. due Jan. '33	i	24	Grandfather	....	10 yrs. ago	40	40	70	70–75	70–75	70–75	70–75	50–33	Normal	7 lbs. 13 oz.	Poor	Toxemia, pyelitis postpartum	
2. F. A. due Aug. '33	ii	23	0	1931—9½ lb. living child	6th mo. of this preg.	...	..	..	..	52	60	64	20	Normal labor induced by castor oil and rupture of membranes	8 lbs. 7½ oz.	Poor		
3. M. K. due Sept. '33	v	41	0	3 9½ lb. living children 1929—died at 10 d. (last preg.) of atresia of bowel	4 yrs. ago during last preg.	...	0	0	0	0	0	0	0	Normal	10 lbs. stillborn	....	Bell's palsy	
4. E. O. due Sept. '33	iv	32	1 sister	1924—7 lbs., lived 12 hrs. 1925—11¼ lbs., stillb. 1926—Cesarean for toxemia, live child, 6 lbs.	3 yrs. ago (5 yrs. after last preg.)	Had req. as much as 55 units; at beg. of preg. 8–10	8, 16, 24 Poor control, patient uncooperative		28	..	32	14	0	0	Cesarean and sterilization	7 lbs. 13 oz.	Poor	Toxemia, severe	
5. L. J. due Dec. '33	i	24	Father Brother Sister	....	Found at beg. of this preg.	...	..	..	15	60	60	0	0	Normal	7 lbs. 1½ oz.	Poor	....	Admitted 10 days before due; needed no insulin
6. I. M. due Nov. '33	vi	36	Mother and sister died of diabetes	1917—premature 4½ lbs., died 1918—10½ lbs., L. and W. 1920—12 lbs., L. and W. 1920—13½ lbs., stillb. 1928—12½ lbs., L. and W.	7th mo. of this preg.	...				20	20	20	10	Normal	7 lbs. 15 oz. ?congenital ht. disease	Poor	Bell's palsy	Entered with acidosis (bronchopneumonia)
7. D. A. due June '34	i	23	0	....	5 yrs. bef. preg.	48	48	40	60	60	60	60	60–32	Normal	7 lbs. 14 oz.	Good, then scanty	Pyelitis postpartum	Required 60 units postpartum until pyelitis subsided
8. M. G. due Aug. '34	iv	36	Brother	1926—5 mos. stillb. 1928—15 lbs. stillb. 1931—diabetic preg. Poor treatment, stillb.	3 yrs. ago	32	32	32	32	85	75	75	30	Cesarean, spinal	10 lbs. Two weeks from term	Poor	....	Entered showing ++++ acetone; under 7 months. preg. when seen
9. M. N. due Feb. 5, '34	iv	29	..	1927—normal, L. and W. 1930—8 mos., stillb. 1932—7 mos., stillb. poor management	12 yrs. ago	10	10–20 units		10–20 units		10–20 units		70–22	Normal	5 lbs. 9 oz. stillborn	..	Entered in coma. Fetal movements present until 1–2 hrs. before entry	On admission, no fetal heart heard. Not seen before admission in coma
							Poor management											
due July '34				1930—misc. 1931—toxemia, live baby, 7 lbs. 1 oz.										extraction			found when 7 mos. preg.	

	During preg.	Nov. del.
0	143	116
½	222	167

due July '34				1930—misc. 1931—toxemia, live baby, 7 lbs. 1 oz.														

11. I. V. due Feb. '35	iv	35	0	1930—9½ lbs., stillb. 1932—13 lb., stillb. 1933—? died at birth	Discovered after deliv.	0	0	0	0	0	0	0	170–0	Cesarean	11 lbs. 3 oz. ? mental retardation	0	B. coli septicemia	Transferred to Beth Israel Hosp. Got well
12. M. M. due July '35	i	30	0	....	During 6th mos. of preg.	...	...	..	...	50	50	...	10	Normal	8 lbs. 10 oz. Macerated. P.M. showed large ht. with glycogen infiltration	0	Hydramnios	Patient preg. again now†
13. D. R. due Aug. '35	iv	39	0	1918—7½ lb., L. and W. 1920—3 mos., miscarr. 1921—10 lb., L. and W. 1926—miscarr. 1931—7½ lb., died later, congen. heart 1931—10 lb., died at 1 day of intracran. hem.	2 yrs. ago	0	0	0	0	32	40	50	0	Normal	10 lbs. 11 oz.	+	0	Baby had erythroblastosis with recovery
14. D. M. due Nov. '35	vii	31	0	1924—6½ lb., L. and W. 1925—5 lbs., L. and W. 1927—6½ lbs., L. and W. 1928—miscarr. 1930—6 lbs., L. and W. 1932—3½ lbs., L. and W.	Prob. during last preg.	15	15	18	18	30	30	36	16–0	Normal	7 lbs., 14 oz.	++	0	
15. S. L due Aug. '35	ii	38	Mother	1933—6¾ lbs., died of erythroblastosis	During 7th mo. of this preg.	...	...	...	...	...	10	20	0	Normal	8 lbs.	0	0	
16 B. S. due Sept. '35	iii	36	0	1920—7 lbs. 1922—7½ lbs.	During 6th mo. of this preg.	...	...	...	...	0	0	0	0	Normal	7 lbs. 6 oz.	0	0	
17. B. D. due Feb. '36	iv	38	0	1920—9 lb. baby crippled at birth 1925—12½ lbs., L. and W. 1929—9 lbs., L. and W.	During 8th mo.									Normal	10 lbs 11½ oz.	++	0	SUGAR TOLERANCE During preg. / After del. 0 102 / 102 ½ 277 / 256 2 222 / 204 3 123 / 80
18. M. T. due Apr. '36	ix	40	0	1916—7½ lbs., prem. 1918—9½ lbs., L. and W. 1923—stillb. twins, 7 lbs each 1924—15 lbs., died at 11 yrs 1925—10 lbs., died at 14 mos. 1927—10.4, L. and W. 1930—7 lbs., L. and W. 1931—9½ lbs., L. and W.	During 8th mo.	...	...	...	...	...	...	...	...	Normal	10 lbs. 12 oz.	++	0	SUGAR TOLERANCE During preg. / After del. 0 164 / 92 ½ 256 / 133 2 286 / 123 3 159 / 82

* All babies alive and well unless otherwise stated.

† Patient delivered normally on July, 1936, of 9 lb., 2 oz. baby.

that pregnancy in pancreatectomized dogs was not accompanied by a decrease in insulin requirement.

The findings in our 18 cases are shown in Table 1. Six of these patients had a family history of diabetes, and of the 6, 3 had diabetes before they became pregnant. Twelve cases required 20 or more units of insulin a day and 1 needed as much as 85 units a day, thus classified as moderately severe. Four were sufficiently mild to be diagnosed definitely only after a sugar tolerance test. With the exception of those cases that never needed insulin, the insulin requirement of all patients increased during pregnancy. Case 4, however, needed less insulin as gestation advanced, probably because she was more coöperative than before her pregnancy. The rise in insulin requirement was often sudden. This shift occurred in the middle trimester, usually at about 5 months. Cases under competent management would suddenly show increased glycosuria and acetonuria. For this reason, it was necessary to admit Cases 7 and 8 to the hospital. In a few instances, insulin reactions occurred just before term and the dose was therefore reduced slightly. After taking 60 units a day during pregnancy Case 5 became sugar free without insulin 10 days before term. This case illustrates the necessity for weekly observations to make adjustments in insulin requirement.

All of our patients needed less insulin in the puerperium. *In no case was the diabetes more severe than before delivery.* We may assure the diabetic woman not only that pregnancy will not increase the risk to her life, but also that it will not make her diabetes worse.

Management of the Diabetes During Labor. The diabetic should be seen by both the internist and obstetrician as soon as she starts in labor and constantly until after she is delivered and out of danger. She should be kept free of acetone. Since ketosis is easily developed in the normal pregnant patient it is even more readily produced in the diabetic. During labor the urine is tested every 2 hours and insulin given according to the amount of sugar found. In the early first stage, when the patient is able to drink, fruit juices and insulin are given. If acetonuria is present 500 cc. of 15% glucose is administered intravenously unless we are sure the patient can take fluids and carbohydrates by mouth. In all cases, except the very mild ones, before leaving the delivery bed, the patient is given normal saline by hypodermoclysis and from 300 to 500 cc. of 15 to 20% glucose intravenously.

Method of Delivery. All diabetics, of whatever severity, unless they present obstetrical abnormalities, are delivered through the pelvis, and normally if possible. Toward the diabetic who has a large fetus we allow a greater latitude. Upon her we perform a Cesarean section a week or 10 days before term. The indication in such a situation is one of relative dystocia, and has no bearing on her medical condition. In the early group of 34 diabetics at this

hospital, Cesarean section was performed 5 times; in the later group of 18 cases, under present discussion, it was performed 3 times, an incidence for the combined series of once in every 8.75 diabetic pregnancies. The three Cesarean sections done in our group of 18 were done for large babies in 2 cases, and for previous section in 1 case.

In deciding on abdominal delivery for a diabetic patient, or for any woman, the operator should weigh well the risk to the mother. In 10 years at this hospital, 1025 Cesarean sections were performed. The maternal mortality from surgical causes, such as hemorrhage, peritonitis, intestinal obstruction and pulmonary embolism was 2.7%, or 1 death in 45 operations. In 10 years in the out-patient department there were 11,608 deliveries which were all normal, low forceps, breech extraction or internal podalic version. The maternal death rate was 1 case in 2902 deliveries. Regardless of diabetes, it is therefore evident that Cesarean section has proved intrinsically 65 times as dangerous to the mother as pelvic delivery. Much thought should be taken regarding the necessity for abdominal delivery in every case, and it should not be selected as an alternative for the normal process of parturition whenever such an outcome may reasonably be expected.

Lactation. The supply of breast milk was insufficient in all of our cases in spite of extra calories added to the diet to compensate for the 500 calories lost daily in the milk. We do not know the explanation of this deficiency. The same phenomenon was found by Markowitz and Soskin in diabetic dogs.

Summary and Conclusions. 1. Under proper management, the diabetic mother may be expected to go through pregnancy and labor safely. Diabetes is usually worse during pregnancy. As a rule there is a sudden decrease in tolerance in the middle trimester which must be compensated by increased insulin. The patient must be checked often during pregnancy. After the pregnancy the insulin requirement returns to the ante-pregnant level.

2. The outlook for the fetus is poorer than in non-diabetics. In the last 4 years, however, the gross and net fetal mortality have been decreased by half.

3. Careful combined medical and obstetrical supervision offers the best outlook for the fetus.

4. The nearest approach to normal delivery is desirable. Cesarean section is reserved for those diabetics whose infants exceed the normal weight, or for cases where some other clear obstetrical indication exists. The two stillborns in our series could not have been saved by more radical delivery. Until we know more about the problem, therefore, we cannot ascribe fetal death to delivery from below, or to over-ripening of the fetus. It is only after we have carefully examined enough diabetic stillborns pathologically that we will have the final answer. For the present, we can find no reason

from our experience to believe that diabetes should be an indication for such a major surgical operation as Cesarean section.

The writers wish to acknowledge the interest and suggestions of Dr. W. R. Ohler.

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ADENOMA OF THE ISLET CELLS OF THE PANCREAS WITH OPERATION AND RECOVERY.

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The surgical pathology of hyperinsulinism has been greatly clarified during the past decade. However, as late as 1932, Heyn,[3] speaking of the treatment of hyperinsulinism, stated that the treatment was medical unless "increasing amounts of carbohydrate became necessary; then surgery, even if unsuccessful, must be tried," and that for the present "surgery appears not to be good enough." Whipple and Frantz[4] have recently thoroughly reviewed the literature on adenomas of the islands of Langerhans. Although they collected 75 cases of hypoglycemia, in only 29 were tumors of islet tissue found at operation. Hence, these tumors while fully established in the literature are still regarded as relatively rare.

We wish to report an instance of hypoglycemia due to a pancreatic adenoma in which the diagnosis was confirmed at operation, and the patient made a successful recovery. Certain of the observations made on the patient before and after operation are of physiologic as well as clinical interest, in a lesion which is being recognized with increasing frequency.

Case Report. B. F. M., a white male, aged 34, was admitted to this hospital on September 3, 1935, with headache, convulsions and mental disorders as his chief complaints. He has one sister who is insane and another who has asthma. As a past history, the patient gave general good

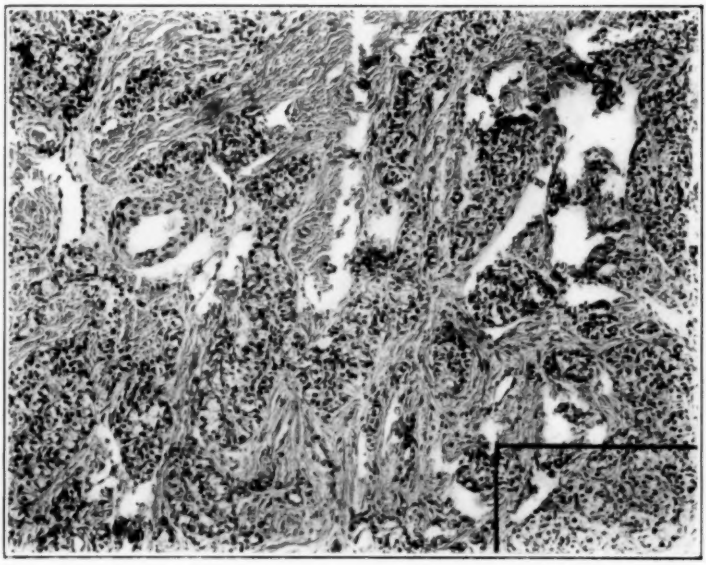

FIG. 1.—Microphotograph of adenoma. × 102.

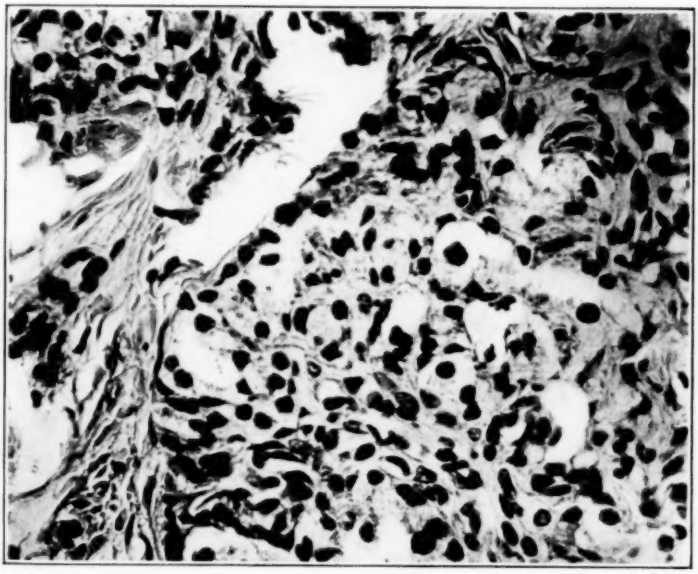

FIG. 2.—Microphotograph of adenoma. × 436.

health with the exception of measles, mumps, chicken pox and diphtheria in childhood. He had an appendectomy at the age of 28. An automobile accident in 1929 caused unconsciousness for 4 hours. He has had asthma and hay fever for the past 5 years. He has never been obese.

Since the middle of July, 1935, he had been having fairly severe, inconstant, headaches. About the same time he had peculiar attacks of mental confusion and disorientation. These included spells of laughter, irrelevant remarks, singing and so forth. It became progressively more difficult to arouse him in the morning. He had had diplopia for 1 day. On August 30, 1935, he went to sleep and could not be roused for 24 hours. When aroused he was quite irrational. Further sleep was followed by a convulsion and vomiting on September 1, and another convulsion occurred September 2, the day before his admission. After this convulsion the blood sugar was 80. He was incontinent of urine September 1 and 2. He was referred to the hospital as a possible case of brain tumor.

Physical Examination. The patient was a tall, well built, well nourished man. On admission he was disoriented, delirious and had hallucinations. Later a wide range of mental symptoms were noted; namely, drowsiness, coma, sullenness and excessive laughter. He never had the slightest memory of any of these episodes after they had passed. Memory was irregular even at best and mental fatigue was noted. For example, stereognosis would be satisfactory for one or two objects, then would fail, but would return after a rest period. There was no evidence of organic neurologic disease. He had a slight fever on admission which led to the tentative diagnosis of encephalitis, but when the spinal fluid was reported negative and the hypoglycemia was discovered he was transferred to the medical ward for study. Here the temperature was 98.2° F.; pulse, 60; respiration, 18; blood pressure, 100/70; and weight, 171 pounds.

There was an occasional extrasystole. The spleen was palpable. Otherwise, physical examination was essentially negative.

Laboratory Findings. Hemoglobin, 103%; red blood cells, 5,600,000; white blood cells, 9700, with a normal differential. Urinalysis was negative. Blood and spinal fluid Wassermann tests were negative. Roentgen examination of the abdomen was negative; the chest showed slight emphysema and increased prominence of the hilum. Blood serum calcium was 10.6 mg. per 100 cc.; serum phosphorus, 3.8 mg.; and cholesterol, 202 mg. The blood sugar findings and the response to various physiologic agents are summarized in Table 1.

TABLE 1.—BLOOD SUGAR STUDIES.

A. Pre-operative.

Procedure.	Fasting.	½ hr.	¾ hr.	1 hr.	2 hr.	3 hr	4 hr.	5 hr.
1.8 gm. glucose per kg. by mouth	48	..	..	175	215	228	175	
Epinephrine 1:1000, 0.6 cc. subcutaneously	89	..	..	83	50	75		
Epinephrine 1:1000 1:2 cc. subcutaneously	30	50	98	147				
Insulin—2 units subcutaneously	30	..	25	25	..	30*		

* Symptoms developed and glucose was given after this blood sugar.

B. Postoperative.

1.8 gm. glucose per kg. orally 9 days after operation	98	..	..	143	106	87	100	66
Epinephrine 1:1000, 0.3 cc. subcutaneously	78	85	88	88				

During his stay in the hospital several attacks of hypoglycemia were observed in which the response to glucose, administered intravenously and

orally, was dramatic. Pre-operatively he was placed on a high-carbohydrate diet of 6 feedings at 4-hour intervals. He was much improved on this, although a morning blood sugar after several days of this régime was 56.

On September 28, 1935, an excision of the adenoma of the pancreas was done. The abdomen was opened through a long, left upper paramedian incision. An incision was made in the gastrocolic omentum and when the bowel had been packed away and retracted the pancreas was readily exposed. No lesion was visible on the surface but when the lower border of the pancreas was mobilized, upon palpation there was found to be a nodule near the tail on the postero-inferior aspect. This lay in the substance of the gland so that a small incision had to be made into the gland before the tumor could be shelled out, silver clips being used to control the bleeding from the parenchyma of the gland.

The tumor measured approximately 1.5 cm. in diameter and was quite firm in consistency (Figs. 1 and 2). Bleeding from the tumor bed having been readily controlled, the incision in the mesentery was then closed with catgut and the abdominal wall closed in layers with catgut in the muscles and fascia and clips in the skin.

Two cigarette drains were inserted to take care of the drainage from the site of removal of the tumor.

The patient's immediate condition after operation was highly satisfactory. The operation was completed at 10.50 A.M. and he was immediately given venoclysis of normal saline and 5% glucose at a rate of 180 cc. per hour. The blood sugar at 12.15 P.M. was 252 mg.%. During the afternoon the urine contained approximately 3.5% of sugar.

The venoclysis was terminated at 4.30 P.M., but the blood sugar remained elevated, being 194 mg.% at 9 P.M. At 10.15 P.M. the urine sugar was 3.3%. He was given 10 units of insulin at 11.30 P.M., and by 6.30 A.M. there was no sugar in the urine and the blood sugar was 118 mg.%. The fasting blood sugar on September 30, 2 days after operation, was 107 mg.%, and the urine was free of sugar. During this period the pulse rate varied from 50 to 90 and there were frequent extrasystoles. On October 8, 1935, the fasting blood sugar was 93 and, on October 12, it was 78 mg.%. The patient was discharged on October 13, 15 days after operation, with complete relief from his pre-operative symptoms.

The data from various studies made during the postoperative period are given in Table 1*B*.

Three months after operation the patient was in excellent health, completely relieved of the disturbances which were present before operation. A word may be said about the effect of this operation on the patient's asthma. Prior to operation he had had, as was noted, "moderate asthma and hay fever for 5 years." He had two fairly severe nocturnal attacks of asthma, relieved by 10 minims of adrenalin, before operation. After operation, there were no attacks which required adrenalin or which elevated the respiration. However, ephedrin by mouth was used to relieve very mild asthmatic symptoms.

One year after operation the patient writes that his asthma has not ceased but is much less severe and less frequent. This he attributed to keeping away from certain feathers and dusts known to aggravate it.

Discussion. Seale Harris,[1] in 1924, suggested that the pancreatic islet cells might elaborate an excess of insulin and give rise to hypoglycemia. The symptom complex of the hypoglycemia due to an islet adenoma was not then understood. It is interesting that the 6 cases observed by Whipple and Frantz[4] personally had been first seen in a neurologic institute where they had gone for nervous and

psychiatric disturbances. It should be stated, however, that the finding of a low blood sugar in association with neurologic or psychiatric symptoms is not sufficient for the diagnosis of pancreatic adenoma.

The patient described had the characteristic mental and nervous symptoms of hypoglycemia, confirmed by the finding of a low blood sugar level at the time of his symptoms. There was temporary response to carbohydrate ingestion and exploration was undertaken with the successful removal of an islet adenoma. The transitory diabetes postoperatively has been observed by others and is presumably a phenomenon of readjustment.

The apparent persistence of asthma after operation is interesting in view of the recent report of Wilmer, Miller and Beardwood[5] on the relation of blood sugar to asthma. The improvement in allergy noted after 1 year is due to better habits of living and affords no evidence that his allergic condition has been relieved by the operation.

Glucose tolerance, adrenalin and insulin tests were carried out at various times. The features of these tests were a diabetic sugar tolerance curve before operation, a possible resistance to adrenalin and no sensitivity to insulin. The occurrence of a diabetic sugar tolerance curve, while not the common finding, has been noted by others. The effect of adrenalin may have been the result of a tolerance developed through its use by the patient in asthmatic attacks. In stating that there was no sensitivity to insulin, the authors have in mind the patient's failure to develop symptoms until 3 hours after its administration, and his ability prior to this time to remain symptom-free at a low blood sugar level. The dose of insulin used here has produced a prompt effect in such insulin sensitive states as Addison's disease. The response of this patient to insulin is similar to that of a normal animal given a small dose of insulin and is in contrast to the severe convulsions which occur in 40 to 60 minutes after insulin is injected in a hypophysectomized animal (insulin sensitive). One would expect this, namely, that the contrainsular mechanisms would be very active in the presence of an insular adenoma and that this would govern the response to injected insulin.

In reviewing these three tests, which have been commonly applied to patients suspected of insular hyperfunction, several things are apparent. Glucose, adrenalin and insulin all influence the blood sugar and each is intended to test a different aspect of the individual's sugar regulation. It is now recognized that varying conditions under which these tests are made will lead to very divergent results. Thus, in states of liver glycogen depletion, adrenalin can produce little or no response, and yet a similar lack of reaction is observed in the glycogen saturated liver in von Gierke's disease. The same types of uncertain response may be found with glucose

and insulin. In all instances, the response is conditioned more by the liver than by the presence or absence of an islet tumor. The recent work of Soskin,[3] showing that the sugar tolerance curve depends on the liver and not at all on the presence of the pancreas, is the most striking demonstration of the fact that alterations of the blood sugar cannot always be regarded as diagnostic of the condition of the pancreas.

It seems then that in these patients the association of symptoms with low blood sugar levels is the criterion which justifies exploration in the event that the symptoms are inadequately relieved by treatment by glucose.

Summary. We have reported the case history of a patient with a pancreatic islet adenoma. The lesion was diagnosed prior to operation and it was removed with complete recovery from the symptoms which it induced. The patient's asthma was not relieved by a return of the blood sugar values to a normal level. Pre-operative and post-operative studies on the effect of epinephrine on the blood sugar and sugar tolerance studies at both stages are discussed.

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TUMOR OF THE BRAIN WITH NORMAL ENCEPHALOGRAM.

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As a rule expanding intracranial lesions produce alterations in the size, shape, and position of the ventricles or an obliteration of the subarachnoid air channels on the side of the neoplasm. These changes depend upon the position, size and nature of the expanding lesion. Since there are so many variations in the "normal," the correct interpretation of air films is beset with difficulties.

In a series of 500 tumors of the brain verified at the Mount Sinai Hospital, in which 120 patients had intracranial air injections, 7 showed normal aërograms. Two other instances of negative encephalograms were found among case records of other institutions (1 from Montefiore and 1 from Bellevue Psychiatric Hospital).

In each one of these cases the conclusion that the encephalogram showed no abnormalities was reached after examination of the plates by the neurologist, neurosurgeon and roentgenologist.

In 8 cases the encephalograms were considered normal and in 1 case the ventriculogram was declared negative for tumor.

Case Reports. Case 1.—S. F., a boy aged 12, complained of occasional attacks of headache, nausea and vomiting for 6 weeks before admission. Twelve days before he entered the hospital, right-sided convulsive movements appeared without any loss of consciousness. Following this attack the patient vomited. These seizures recurred a number of times during the 2 days before his admission.

The examination showed a brachiofacial paresis with pyramidal tract signs on the right side. There was a slight defect in the periphery of the upper quadrant of the right temporal field of vision. The fundi were normal. A lumbar puncture showed an initial pressure of 120 mm. of water. Nine days after admission an encephalogram showed normal size, shape and position of the ventricles and a moderate amount of air in the subarachnoid spaces on both sides. Two weeks after the encephalography a craniotomy was done. A tumor, 3 cm. in diameter was found in the left paracentral lobule. The histologic diagnosis was spongioblastoma multiforme. Two weeks after craniotomy the patient was discharged as improved.

Comment. The diagnosis in this case was based entirely on the clinical findings. Because there were no signs of intracranial hypertension, this patient was subjected to an encephalogram. The negative air studies delayed operative interference until definite progression was noted.

Case 2.*—A. B., male aged 44, was admitted to the Bellevue Psychiatric Hospital on March 16, 1935, because of mental symptoms. Six months before admission the patient began to complain of vague abdominal pains and headache. Several abdominal laparotomies were performed without relief. Two weeks before admission the headaches became more severe, his vision became blurred and he became irritable and confused.

The examination showed an ataxic gait; bilateral ptosis, more marked on the left side, was present; slight nystagmus on looking to the right and marked upward and downward impairment of conjugate gaze were noted. The pupils were equal and slightly irregular, though they reacted to light and in accommodation. There was some cogwheel rigidity in the right upper limb. The fundi were negative. He was lethargic, bewildered and confused. The lumbar puncture showed a normal pressure, clear and colorless spinal fluid with 27 lymphocytes per c.mm. Eleven days after admission an encephalogram showed normal ventricular and subarachnoid systems. The patient became progressively worse and stuporous, and died 1 month after admission.

The autopsy disclosed no evidence of increased intracranial pressure. The ventricular system was normal. There were apparent softenings of the tip of the left corpus striatum, the right globus pallidus, the median portion of the putamen and in the substantia nigra. No other gross lesions were found. Sections through these areas showed an unclassified primary tumor of the brain, probably of the nature of a sarcoma. The tumor tissue was infiltrating and invaded the basal ganglia and the floor of the third ventricle.

* This case report is published through the courtesy of Dr. K. M. Bowman, Director, Bellevue Psychiatric Hospital.

Comment. This case illustrates the presence of a normal ventricular system not only by encephalogram but at autopsy. The interesting feature is the presence of an infiltrating tumor without evidence of intracranial pressure in the region of the floor of the third ventricle and aqueduct where one would expect an early obstruction to the flow of the cerebrospinal fluid.

CASE 3.—W. A., a man aged 50, was admitted to the Mount Sinai Hospital with a history of convulsive seizures for 26 months. During this period he became more irritable and quarrelsome. Seven months after the onset of his illness he was considered a "brain tumor suspect" in another hospital. An encephalogram at that hospital revealed a slight increase in the subarachnoid spaces. This suggested a degenerative process at the time. The ventricular system and the basal cisterns were declared to be normal. Because of the relatively negative encephalogram, he was discharged with the diagnosis of encephalitis. Two weeks after discharge and 18 months before his admission to the Mount Sinai Hospital he had "hives" and then developed twitchings in the left side of the body followed by a progressive left hemiparesis. For the last 6 months before his death he noted that when he grasped an object with his left hand he could not release the object at will.

The examination at the Mount Sinai Hospital revealed definite euphoria, a left spastic hemiparesis, and a left forced grasping reflex. The fundi were normal. An encephalogram showed a shifting and distortion of the ventricular system due evidently to a tumor in the right parasagittal region. An exploratory craniotomy disclosed a glioma the size of an orange in the right paracentral lobule.

Comment. The slight increase in the subarachnoid markings, if pathological, was not caused by the proven expanding lesion. This patient was under constant observation by many excellent neurologists and roentgenologists. (During the earlier stages of a brain tumor the aërogram may be negative.)

CASE 4.—C. B., a male aged 38, was admitted to the Mount Sinai Hospital with the main complaints of headache and a speech disorder. Sixteen months before, following a brief prodromal period of headache and dizziness, he had a convulsion with very transitory impairment of speech. Five months later a left facial paralysis appeared. This persisted for 2 weeks. The patient was well again up to 4 months before admission when he had a fleeting attack of dizziness and unsteadiness in gait. Two months later he complained of vague gastro-intestinal distress and headache. This was soon followed by difficulty with speaking and an inability to understand what was said to him. The speech impairment became worse and he soon began to fear that someone would harm him. He was anxious and restless. Severe headache with frequent nausea were present throughout the illness. He again improved and became symptom-free until 1 week before admission when all symptoms reappeared.

The examination showed a slight right lower facial weakness. The fundi were normal. The patient was spontaneously overtalkative, and appeared frightened. Lumbar puncture showed a normal initial pressure. The clinical impression was that of a tumor in the left temporal lobe. During his residence in the hospital he improved. Two weeks after admission he was discharged to the care of his family physician.

Three weeks later he was readmitted because of severe headaches and inability to recall names of simple objects. Examination this time showed

FIG. 1.—Normal encephalogram with verified brain tumor. Case 2.

slight tremor of both hands, a suspicious left Babinski and a right lower facial weakness. He was confused; his memory for recent events was poor; there was an anomia; he was unable to do simple calculations and he found it difficult to obey complicated commands. A right homonymous hemianopsia was noted on perimetric examination.

Because of the complete remissions and exacerbations the patient was thought to be suffering from an aneurysm. A Roentgen ray of the skull revealed a calcified pineal gland in the normal position. The anterior clinoids of the sella turcica were slightly eroded. One week after admission an encephalogram showed large globular collections of air in the subarchnoid spaces but no air in the ventricles. Four days later the hemianopsia disappeared and 8 days after the encephalogram a ventriculogram was performed and showed normal size and position of the ventricular system. The patient continued to improve and on discharge 6 weeks after his admission all examinations gave negative results.

Six months after leaving the hospital the patient was readmitted because of an attack of tremulousness, recurrent confusion, inability to speak and a convulsive seizure. On the day following this admission a ventricular puncture was performed. No fluid could be obtained from the left side. Two days later no tumor was found during a left exploratory craniotomy. The autopsy disclosed a granular round mass 3 cm. in diameter in the region of the left angular gyrus. This tumor proved to be a cavernous angioma.

Case 5.—I. M., a man aged 30, was admitted to the Mount Sinai Hospital with a history of a head tremor for 15 years. In addition, twitching of the limb on the left side was reported for 8 years. Five years before admission a grand mal seizure was observed for the first time. These convulsive seizures recurred and were frequently precipitated by undue mental strain or emotional stress.

The examination showed a mild left lower facial weakness with diminished sensation on the left side of the body. The left knee jerk was slightly more active than the right. The fundi and visual fields were normal. Eight days after admission an encephalogram was performed and an irregular calcified mass was found to be situated 1 inch behind the coronal suture on the right side near the dura. The ventricles were found to be symmetrical and uniformly slightly enlarged but there was no shift. The subarachnoid spaces and the basal cisternæ were normal. The patient left the hospital against advice. One year later a Roentgen ray of the skull showed the calcified mass to be slightly larger than on the previous examination. A calcified pineal was found in its normal position. There was no evidence of increased intracranial pressure. Except for a questionable bilateral early papilledema the physical findings were the same as those on the previous examination. An exploratory craniotomy was subsequently performed and a calcified tumor was removed from the right parietal lobe. Histopathologically, the tumor was a calcified glioma.

Comment. Normal ventricular and subarachnoid systems existed during the course of a brain tumor with definite calcification which increased in size during the course of observation. Slight symmetrical dilatation of the ventricles has questionable pathologic significance.

Case 6.—L. Z., a 39-year-old housewife, entered the Mount Sinai Hospital complaining of headache. Two years before admission she experienced intense generalized headaches. Seven months before admission, after a mentally retarded son was sent to an institution, she became worse. She was depressed and lost interest in her surroundings. She had recurring

periods of confusion. After 2 months these mental changes cleared up. Two months before admission the mental symptoms reappeared. One month later weakness of the left upper limb set in, to be followed in a few days by the feeling that someone was sitting at her left side and that she was holding something in her hand.

The examination revealed a slow, cautious gait with decreased associated movements of the left upper limb; the left palpebral fissure was slightly greater than the right; the left pupil reacted consensually but was fixed to direct light; the fundi showed early papilledema, more marked on the left side; she was dull; psychomotor retardation, confusion, defective memory and emotional instability were present. The mental picture was that of an organic psychosis. A Roentgen ray of the skull was negative. The lumbar puncture showed xanthochromic fluid under an initial pressure of 160 mm. of water with 40 lymphocytes per c.mm. and a total protein of 270 mg. per 100 cc. Twelve days after admission the encephalography showed a normal ventricular system. The subarachnoid spaces were not visualized well on either side. A few days later the patient left the hospital against advice. An encephalogram performed 1 month after discharge showed the ventricular system to be displaced to the right and a craniotomy revealed a left parietal lobe glioma.

Comment. This case illustrates the fact that a patient with a tumor of the brain may have papilledema and at the same time a normal ventricular system. The clinical diagnosis was tumor of the brain but there were insufficient signs for localization. Since the aërogram was negative for tumor, operation was delayed until a subsequent encephalogram showed a shift of the ventricles to the right. The decreased amount of air in the subarachnoid spaces on both sides may be considered a normal variation.

CASE 7.*—B. K., a male aged 45, was admitted with the chief complaints of stiffness and weakness in the right arm and leg. For 18 years before admission, the patient had suffered with severe frontal headaches. In 1922, 12 years before admission, the right upper extremity suddenly became weak. Following this episode, the right side of the body became progressively weaker. During the last year before admission there were a few convulsions. He became emotionally labile, depressed and irritable.

The examination showed a right hemiparesis with motor aphasia. The fundi were normal. An encephalogram done at another hospital revealed a slight uniform dilatation of the entire ventricular system. A definite diagnosis could not be made. The patient was discharged for observation. One year later, the patient was readmitted with bilateral papilledema. The encephalogram on this occasion showed a slight shift of the ventricular system to the right with an obscuration of the left inferior horn. Craniotomy and subsequent autopsy disclosed a vascular tumor (hemangioendothelioma) in the region of the left corpus striatum, hippocampus and island of Reil.

Comment. The operation was delayed because there was no evidence of an expanding lesion by encephalogram. A slight dilatation of the ventricular system is frequently found in conditions other than tumor and as previously stated may be considered a normal variation.

* This case report is published through the courtesy of Dr. S. P. Goodhart, Attending Neurologist, Montefiore Hospital.

CASE 8.—A. C., a 42-year-old housewife, was admitted to the Mount Sinai Hospital with the history of recurring attacks of dizziness, nausea, and fainting since her 23d year. Attacks of mild headache had also been present. These complaints were attributed to a head injury sustained 13 years previously. At the age of 32 "she was operated on the left side of the head." She improved, and for 8 years was symptom-free. Two years before admission the fainting spells recurred; 6 weeks before admission vision became impaired and 3 weeks later she had a generalized convulsion.

The examination showed bilateral papilledema with hemorrhages, generalized hyperreflexia, and a positive left Babinski. A Roentgen ray of the skull showed an old trephine opening in the left parietal bone.

An encephalography was unsuccessful. A few days after this air injection the patient became stuporous, and an emergency right subtemporal decompression was performed. The result was a remarkable improvement with almost complete recession of the papilledema.

She was discharged as improved and was in good health for 10 months. She then suddenly became comatose. This was followed by a transitory right hemiparesis. The examination on the second admission revealed low grade bilateral papilledema and a positive left Babinski. Smell was impaired bilaterally. Under observation she had a generalized convulsion. An encephalogram revealed normal ventricles and subarachnoid spaces. Since the suspected tumor could not be definitely demonstrated, the patient was discharged to the Follow-up Clinic. She was watched there for 2 years. Convulsive seizures recurred about every 3 months. Impairment of memory became more marked during the year before her last admission.

When she was readmitted a third time, 3½ years later, the only objective signs were a slight blurring of the right optic disc margin and bilateral hyposmia. A third encephalogram showed a questionable shift of the ventricular system to the left side and a shadow which was interpreted as a calcification in the right subfrontal region. Because of this calcific shadow the right frontal lobe was explored and a hemangiomatous tumor involving two-thirds of the right pre-frontal lobe was excised.

Comment. It was difficult to understand the existence of choked disks in the presence of a normal ventricular and subarachnoid system. Despite the fact that the patient had had bilateral subtemporal decompressions, changes in the ventricular system should be expected where papilledema existed.

In this case, the excessively long remissions in symptoms, the absence of headache, the paucity of physical signs, and negative air studies, all tended to exclude an expanding intracranial lesion, although the total impression of the clinical picture and the course of the disease pointed to what proved to be the correct diagnosis.

CASE 9.—S. H., a male aged 59, entered the Mount Sinai Hospital with a 4-months' history of convulsions. Fifteen years before admission a hemangioma of the lower right lip was excised but had recurred. The present illness began 4 months prior to admission when the patient suddenly became aware of a clonic twitching of the left side of the body which began in the left wrist and spread upward to involve the whole left side of the body. Following this attack the left side of the body was paralyzed for 2 hours. There were numerous similar attacks since the onset of the present illness.

The examination revealed a spastic paralysis of the left arm and a flaccid paralysis of the left leg with tendon hyperreflexia, absent abdominals and

loss of plantar flexion on the same side. The fundi were normal. The blood pressure was 160/100. The lumbar puncture showed an initial pressure of 160 mm. of water. He was depressed and anxious.

The clinical diagnosis was tumor of the right frontal lobe. Five days after admission a right frontoparietal exploratory craniotomy was done but no tumor was found. Two weeks following the operation an encephalogram was performed during which 110 cc. of fluid were removed and 90 cc. of air injected. Both ventricles were found to be normal in size and shape. There was a question whether the right lateral ventricle was on a slightly lower level than the left. The third ventricle was normal in size and position. The diagnosis of an expanding lesion could not be made after examination of these aërograms.

The patient continued to improve. The left hemiplegia disappeared almost entirely. Twenty days after the craniotomy he was discharged from the hospital with instructions to return if any new symptoms appeared. Despite the negative encephalogram and improvement in symptoms the provisional diagnosis was right frontal lobe tumor.

Seventeen days after his discharge from the hospital the patient was readmitted because of right-sided headache, restlessness, retention of urine and increasing stupor. The examination on this admission revealed the same positive findings as during his previous residence in the hospital. Eight days later the patient was reëxplored. A transitional cell glioma (6 by 4½ by 3 cm.) was removed from the right paracentral lobule. Two weeks after operation the patient was discharged from the hospital. He died at home 3 months later. No autopsy was obtained.

Comment. The diagnosis of tumor of the brain on admission was based on a clinical course. Since the first exploratory craniotomy revealed no tumor, an encephalogram was performed for more precise localization. This was of no aid. The slightly lower position of the right ventricle probably had some significance but it was insufficient to warrant a confirmatory diagnosis of the presence of a tumor, even after a consideration of the clinical history in this case.

Tumors of the brain, irrespective of their location, nature, size and rate of growth, may exist for a long time without significant alterations of the ventricular and subarachnoid spaces. In this group, the locations of the neoplasms were as follows: 3 were in the parietal lobe, 4 in the frontal lobe, 1 in the corpus striatum and temporal lobe and 1 in the basal ganglia. The histologic nature of the tumors was as follows: 3 hemangiomata, 5 gliomata and 1 sarcoma. The duration of the course of the disease up until the time a normal encephalogram was found varied from 2 months to 19 years. In most instances the course was protracted. In 4 cases papilledema was found to be present while the ventricular system was normal. In 8 cases the operation was delayed because the encephalogram was normal. In 9 cases the clinical signs were sufficient for localization and diagnosis of tumor. Two patients showed calcifications in the tumor in the presence of "normal" encephalograms. One patient had a normal encephalogram and at autopsy normal ventricles, despite the fact that the tumor was located in the corpus striatum.

The wider use of air injections for the diagnosis of intracranial

disease and the recent emphasis on the importance of early diagnosis of tumor of the brain will undoubtedly lead to the more frequent finding of normal encephalograms in cases of brain tumor.

The literature on this subject is extremely meager. Dahl-Iversen[1] reported a case of papillomatous tumor of the fourth ventricle with papilledema and with a normal aërogram after ventriculography. The autopsy confirmed the absence of dilatation of the ventricular system. We have not been able to find other cases.

The interpretation of slight variations in the aërogram is beset with difficulties because of the relatively frequent incidence of such deviation from the accepted normal. It is doubtful whether slightly diminished subarachnoid markings or a mild indentation or diminution in size of a ventricle will by and in itself justify exploration. A slight depression was found in the anterior part of the left lateral ventricle in Dahl-Iversen's case though the tumor was in the posterior fossa. Goette[2] has collected the known information on the variations of the normal aërogram. He concludes that there are many abnormalities which are within normal limits. Kornblum and Grant[3] state that: "Encephalograms performed upon the same individual at different times under apparently normal conditions may vary markedly in the size and shadows representing the subarachnoid spaces." Slight variations assume significance only when the clinical findings suggest an expanding lesion in a particular part of the brain.

It must be distinctly understood that the designation "normal" depends on the concept of normalcy of the aërogram at the time of the diagnosis. It is likely that further study of the encephalogram in tumors will reveal significant changes the importance of which has been overlooked.

Summary. 1. A series of 9 cases of brain tumor with normal aërograms is reported.

2. Normal ventricular and subarachnoid systems may exist irrespective of the nature and location of the tumor and the duration of its course.

3. Attention is called to the fact that a negative encephalogram does not exclude the diagnosis of a tumor based on clinical grounds.

4. During the earlier stages of a brain tumor the aërograms may be negative.

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VISCERAL PATHOLOGY IN MEASLES.

A CLINICO-PATHOLOGIC STUDY OF 100 FATAL CASES.

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MEASLES has long been recognized as a serious and frequently fatal disease, and the pathology of this condition has been the object of much study and investigation. Most of the studies, however, have concentrated on one organ or group of organs, particularly the respiratory tract and the nervous system. This is an attempt to study the general pathology found throughout the body in a large series of measles deaths. It consists of 100 autopsies, 94 from the laboratory files—3 previously reported[5,8,10], and 6 personally performed. For most of those on file, it was difficult to give satisfactory gross descriptions; accordingly, the references to the gross pathology are for the most part brief quotations, the chief emphasis being placed on microscopic findings.

Pathologic Anatomy. *Heart and Pericardium.* Pericarditis was present in 4 cases. Two showed a shaggy exudate on the visceral pericardium with the pericardium distended with purulent fluid, while 2 had lesser amounts of purulent fluid and no fibrinous exudate. Pericardial effusion was somewhat more common, 13 cases showing effusion of clear fluid, 3 of 50 cc. or over and 10 of 15 to 50 cc. The heart itself showed no characteristic gross changes. Dilatation of the right heart in varying degree was found 24 times.

Of 91 hearts examined microscopically, only 4 showed more than the usual toxic changes. These 4, including the 2 with exudative pericarditis, had cellular infiltration of the myocardium. The infiltration was chiefly lymphocytic, and was partially, but not predominantly, perivascular in distribution.

Pleura. Involvement of the pleura was noted in 27 cases. Empyema occurred in 13, 2 bilateral and 11 unilateral. A well marked fibrinous pleuritis, excluding those cases showing only a few fresh fibrinous strands, was found in 14 cases, 5 with serous effusion and 9 without effusion. Bilateral pneumothorax, with associated bullous emphysema of the anterior mediastinum, was seen once, death having occurred 4 hours after a tracheotomy.

Lungs. Pneumonia of sufficient extent to be recognizable grossly was present in 93 cases. Of the 7 showing no gross pneumonia, 3 also had none by microscopic examination, and 3 only a mild incipient process. The gross process had mostly a patchy lobular distribution.

Microscopically, the process was chiefly of 2 types. The interstitial type, the more usual, consisted of a marked thickening of the bronchial and alveolar walls, with a thin exudate of serum and

phagocytes in the alveolar lumina. The lobular type showed a heavy purulent exudate, consisting almost entirely of neutrophils and fibrin, with distention of the alveoli and consequent thinning of their walls. The bronchi and bronchioles in almost all the sections in both classifications contained purulent exudate. This, as a rule, did not invade the walls, although the epithelium usually exhibited a catarrhal desquamation, indicating the presence of an acute bronchitis and bronchiolitis. The bronchial walls were for the most part intact, although there was usually some slight peribronchial lymphocytic infiltration.

In most instances both types were present, but often one or the other greatly predominated. The predominating variety was interstitial in about one-half of the cases and lobular in about one-sixth, while the remainder had a fairly equal distribution of both varieties. The earliest cases were of the peribronchial interstitial type.

The most unusual lung finding was in a case in which death was apparently caused by a large infarction of the right upper lobe. The lesion proved to be due to complete occlusion of the branch of the pulmonary artery supplying this lobe by pressure from several enormously enlarged, non-tuberculous lymph nodes.

Larynx. The larynx in practically all cases showed slight to moderate congestion and edema, but in 13 the changes were excessive. Of these, 9 presented an extremely severe laryngitis, 6 showing ulceration (involving the vocal cords in 3), and 3 a membrane. The remaining 4 cases, though without membrane or ulceration, had sufficient congestion and edema to cause respiratory difficulty and death from obstruction.

Microscopically, sections were available in 4 of these severe cases. All showed an acute inflammatory process, with thrombi in the veins and large deposits of fibrin, and in 3 the inflammatory changes were widespread, the fibrin deposition being even more pronounced in the deeper layers than on the surface.

Of these 13 cases, it is of interest that 8 were typical cases of measles croup, with death clinically due to laryngeal obstruction. Two had no note on the chart concerning a laryngeal inflammation, while 3 had only mild clinical laryngitis. Of the 13, nose and throat cultures were negative for Klebs-Loeffler bacilli in 9, while in 4 there were no nose and throat cultures reported.

Trachea. The trachea and primary bronchi were almost uniformly deeply injected, with a reddened mucosal surface and usually a mucoid secretion. No membrane was observed, other than in the upper few centimeters as a direct extension from a laryngeal membrane. Microscopically, the usual picture was an intense congestion of the mucosal vessels, and a mild lymphocytic infiltration, usually involving neither the epithelium nor the glandular layer but diffusely infiltrating the area between. Of the 22 sets of sections

examined, 13 were of the type just described, while 9 ranged from slightly greater inflammatory change with some invasion of the glands to a severe inflammation with necrosis and epithelial sloughing.

Thymus. Satisfactory figures on the gross appearance of the thymus could not be compiled, but the striking feature of this gland was the microscopic picture. Of sections from 64 cases, 41 showed a marked degree of atrophy with great depletion of the lymphoid tissue. In 34 the Hassall's corpuscles were either greatly decreased in number or entirely absent, while in the remaining 7 there were numerous large corpuscles undergoing marked degeneration. Lymphoid hyperplasia was found only twice. This atrophic process is apparently the so-called accidental involution which is said to occur in many acute infections, and which has been seen in this laboratory in other contagious diseases.

Tonsils. The tonsils were for the most part enlarged and inflamed, but actual gross purulent inflammation was seen in only 2 cases. Microscopically, these 2 were the only ones to show an acute inflammatory process. In both, blood-vessels were seen to pass directly through areas of acute inflammation, and in 1 of them the vessel wall was necrotic, with actual invasion by cocci visible (Fig. 1). There was marked generalized sepsis in both cases, with hemolytic streptococci cultured throughout the body, including tonsils and heart's blood, and the microscopic picture would seem to provide an excellent illustration of the probable portal of entry. Giant cells, as described by Warthin and others[2,6,7,11] in the tonsil and appendix in the prodromal stage of measles, were not found in either organ in our material.

Lymph Nodes. The lymph nodes throughout the body were enlarged and congested, particularly those in the cervical, peribronchial and mesenteric groups. Only 3 showed suppuration. The characteristic microscopic picture was one of *subacute* inflammation. In contrast to the lymphoid hyperplasia in the spleen and intestinal tract, the lymphoid tissue of the nodes seemed decreased in amount, with relatively little lymphoid activity. The vessels were congested, and the sinuses widely dilated and packed with lymphocytes, large phagocytic mononuclear cells, and plasma cells. Fibrin was occasionally seen. Definite *acute* inflammation was observed in only 2 of the 77 sets of sections studied. Extreme congestion was found in 8 cases, 1 of which also showed extensive microscopic hemorrhage. Lymphoid hyperplasia was observed only twice. A mild hyperplasia of the reticulo-endothelial system was not uncommon.

Spleen. The spleen in most instances was considerably enlarged. The characteristic gross appearance was one of marked congestion and follicular hyperplasia; much less often a soft, mushy, septic spleen was found. Microscopically, the typical picture was one of

marked congestion with lymphoid and reticulo-endothelial hyperplasia. Microscopic hemorrhage was seen in 14 cases (marked in 2).

Liver. The liver was generally enlarged, and usually showed gross evidence of cloudy swelling and congestion. Microscopically, the liver sections uniformly showed toxic changes in varying degree, consisting of cloudy swelling, fatty infiltration, and congestion. The congestion was usually marked, but in only 3 instances was there passive congestion to the point of central necrosis of liver cells. The most frequent lesion observed was an infiltration of the portal spaces with lymphocytes (Fig. 2); this was found in 20 cases (22% of those examined). In 11 it was classified as slight, in 8 as moderate, and in 1 as marked. The infiltration did not in any case invade the liver lobules, and was composed almost exclusively of lymphocytes and rare plasma cells. In none of the sections was there a consistent perivascular or periductal arrangement of the invading cells.

Pancreas. No gross lesions were observed in the pancreas. Microscopically, one section of the 74 examined showed a slight, rather diffuse infiltration of the interstitial septa with lymphocytes and plasma cells.

Adrenals. Marked unilateral medullary hemorrhage was found in 1 case. The adrenals were otherwise grossly normal throughout the series. Microscopic medullary hemorrhage was observed in 3 cases, though only in the one just noted was it extreme. Lymphocytic infiltration of the medulla occurred in 3 sections of the 84 examined.

Kidneys. Grossly, the kidneys generally showed congestion and often cloudy swelling. Mild pyelitis and ureteritis occurred in 2 cases, unilaterally in 1 and bilaterally in the other. Microscopically, practically all the cases showed congestion, and also fairly marked cloudy swelling of the tubular epithelium. Of the 95 sections examined, there was a moderate interstitial mononuclear infiltration in 6, without involvement of the glomeruli (Fig. 3). The cells were chiefly lymphocytes, with a considerable number of plasma cells and cells of endothelial character. Both cortex and medulla were affected. In only 3 cases of the 95 was there any evidence of glomerulitis, and in all of these the process was an early one.

Gastro-intestinal Tract. Acute appendicitis was found in 3 instances, 1 with perforation. No other significant gross changes were noted. Microscopic sections of the gastro-intestinal tract were available in only 14 cases, and beside a single appendix section which showed an acute inflammatory process and no giant cells, exhibited only a moderate intestinal lymphoid hyperplasia in slightly over half the cases.

Peritonitis. Peritonitis was found in 5 cases, 3 of which yielded hemolytic streptococcus on culture. A fourth case was due to a

ruptured appendix, and in the remaining 1 the process was limited to the pelvis and was apparently a tuberculous peritonitis.

Brain, Ears and Mastoids. In practically all of the 29 cases in which the skull was opened, the brain showed moderate edema and congestion, and in 5 there were scattered punctate hemorrhages. A cortical abscess, apparently secondary to mastoiditis, occurred once. Purulent meningitis was found in 3 cases, 2 due to hemolytic streptococci. Serous meningitis with opalescent fluid occurred twice, and hemorrhagic softening due to cortical venous thrombosis was seen once.

Otitis media or mastoiditis or both were found at autopsy in 13 of these 29 cases, involving the middle ear alone in 4, the mastoid alone in 3, and both middle ear and mastoid in 6. Sinus thrombosis was found in 4 cases, 3 of these showing an associated mastoiditis.

Microscopically, toxic changes were generally found in the brain, consisting of congestion, pericellular and perivascular edema, and some degree of degenerative changes in the nerve cells. In 5 cases these changes were especially marked, with small hemorrhages into the Virchow-Robin spaces, and perivascular infiltration with mononuclear cells, chiefly lymphocytes, in 1 instance with very definite cuffing (Fig. 4). These 5 cases were interpreted pathologically as early encephalitis, and in 4 of them a clinical diagnosis of encephalitis was made, while such diagnosis was not made in any other cases. No definite demyelinization was found.

Skin. Skin sections were examined microscopically in 11 cases. The only constant finding was slight to moderate lymphocytic infiltration of the corium, sometimes perivascular in distribution, but not uniformly so. Active desquamation of the epidermal cells was occasionally observed. In no instance was there thickening of the cornified layer. Swelling of the endothelial lining cells of the capillaries was noted in 3 sections, and slight subendothelial lymphocytic infiltration in 1. No relationship could be made out between the extent of the microscopic lesions and the appearance and duration of the rash.

Bacteriology (See Table 1). One or more cultures were taken from 74 cases. The most striking feature was the overwhelming predominance of hemolytic streptococci. These organisms were present either alone or with other organisms in 57 cases, or 77% of those from which cultures were taken, and in pure culture, as the only organism found in the body, in 30 cases or 41%. Blood cultures were not taken during life from the majority of the cases, but of the 31 showing a pure hemolytic streptococcus in the heart's blood at autopsy, 5 had similar ante-mortem blood cultures. The only other organisms found in more than one or two cultures were Pneumococcus, Types I and XIV, Strep. viridans, and Staph. aureus and albus.

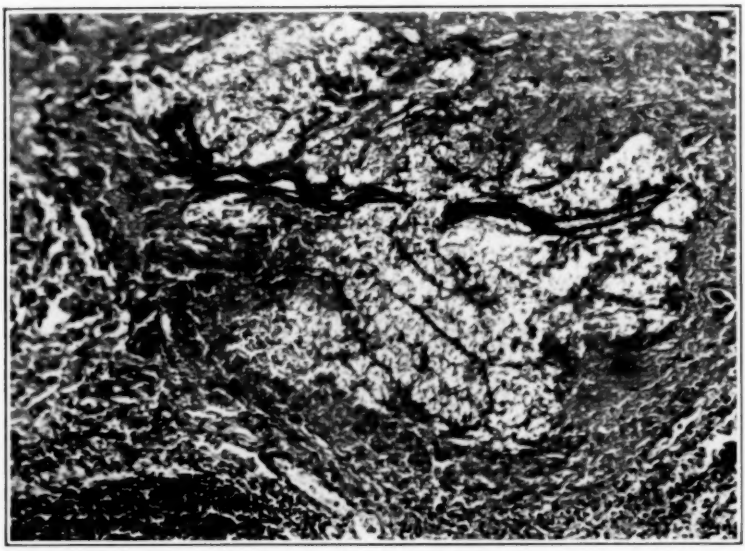

FIG. 1.—*Tonsil.* Acute tonsillitis in measles. Necrotic area with necrosis of blood-vessel. Phloxin methylene blue. × 110. (Under oil immersion, penetration of cocci through the necrotic wall into the lumen of the vessel can be seen.)

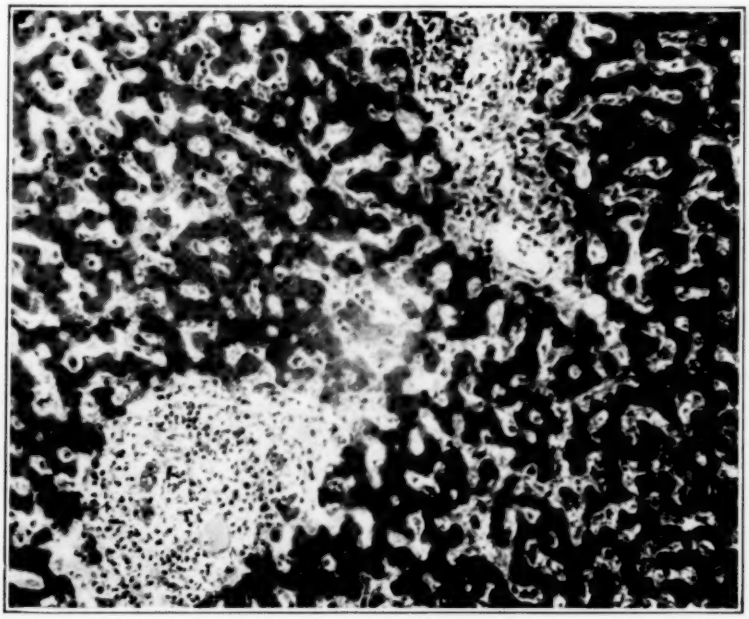

FIG. 2.—*Liver.* Lymphocytic infiltration of portal spaces. Phloxin methylene blue. × 135.

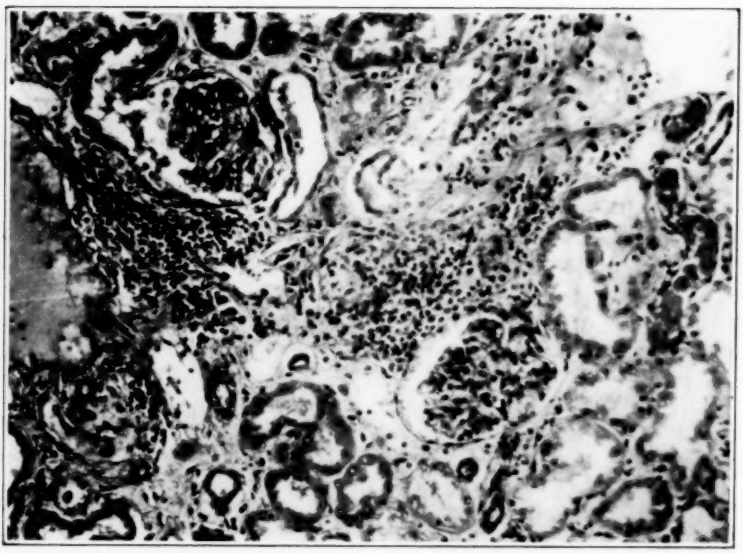

FIG. 3.—*Kidney.* Interstitial infiltration with lymphocytes. Phloxin methylene blue. × 150.

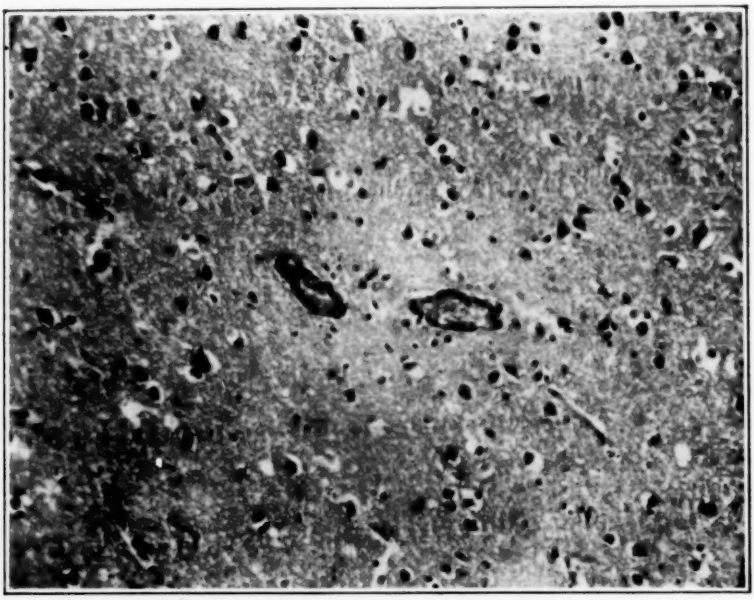

FIG. 4.—*Brain.* Measles encephalitis. Perivascular cuffing. Hematoxylin phloxin. × 215.

TABLE 1.—BACTERIOLOGIC FINDINGS.

	Heart's blood.	Lung.	Chest fluid.	Pericardial fluid.	Peritoneum.	Larynx.	Tonsil.	Testis.	Brain.	Cerebral fluid or exudate.	Spinal fluid or exudate.	Middle ear.	Mastoid.
Number of cultures taken	68	40	15	3	8	4	2	1	3	3	2	3	5
No growth	16	7	1	..	1	..	..	..	1	..	1		
Streptococcus hemolyticus	31	21	6	..	2	2	1	1	1	1	1	2	3
Strep. hem. and Strep. viridans	4	3	3	1	2	2	1						
Strep. hem. and Staph. aureus	4	..	..	..	..	..	..	..	..	1	..	1	
Strep. hem. and Green. strep.*	1	3											
Strep. hem. and Pneumo., Type XIV	..	..	1	..	1	..	..	..	..	..	..	..	1
Streptococcus viridans	1	2											
Pneumococcus, Type I	1	1	1	1	1	..	..	..	1				
Staphylococcus albus	2	3											
Miscellaneous†	8	..	3	1	1	..	..	..	..	1	..	..	1

* Green streptococcus, bile solubility test not done.

† Includes single organisms and groups of organisms not occurring in more than two cultures. These include, in addition to the organisms listed above, Pneumococcus, Types II and IV, Pfeiffer's bacillus, Streptococcus anhemolyticus (gamma), and Bacillus coli (in a case of ruptured appendix).

Clinical Considerations. The age incidence is shown in Table 2. The greatest incidence was in the 18 months period from the sixth month through the second year, 60% falling within this age group. No case occurred under the age of 3 months, and only 2 under 6 months. Only 3 cases were over the age of 8 years, including 1 adult of 40.

TABLE 2.—AGE INCIDENCE.

		Under one year:	
Under 1 year	21	3 months	1
12 to 18 months	24	5 months	1
18 to 24 months	17	6 months	1
2 years	11	7 months	3
3 years	7	8 months	5
4 years	7	9 months	5
5 years	2	10 months	1
6 years	4	11 months	4
7 years	2		21
8 years	2		
10 years	1		
15 years	1		
40 years	1		

The incidence of the chief complications, the day of illness on which they were first diagnosed clinically, and the day of illness on which death occurred are summarized in Table 3. It will be noted that pneumonia was an early complication, occurring in 32 cases by the fifth day, and in 71 cases on or before the tenth day. Laryngitis and encephalitis were also found early in the illness, while empyema, as might be expected, was a considerably later complication. Death usually occurred late in the disease, 77% dying later than the first week. No correlation could be made between the day on which death occurred and the character and extent of the lesions found. Tuberculosis as an incidental finding was seen in 3 cases.

TABLE 3.—DATE OF CLINICAL ONSET OF CHIEF COMPLICATIONS.

Day of illness.	1st.	2d.	3d.	4th.	5th.	6th.	7th.	8th.	9th.	10th.	11–15.	16–20.	21st and over.	Not diagnosed clinically.
Pneumonia*	1	3	6	11	11	13	3	11	8	4	8	3	2	7†
Empyema‡	..	..	..	..	..	..	..	..	..	2	5	2	..	3
Laryngitis	..	1	1	2	3	1	2	..	..	..	..	..	1	2
Peritonitis	..	1	..	..	..	..	..	..	..	..	..	1	..	3
Encephalitis	..	1	1	..	2	..	..	1						
Meningitis	..	..	..	2	..	..	..	..	..	..	..	..	..	3
Day of death	..	..	2	3	3	6	9	7	4	10	21	14	21	

* In 2 cases, pneumonia antedated the onset of measles by 2 and 3 days, respectively.

† On the basis of gross pneumonia at autopsy.

‡ One case of empyema died in ambulance on 10th day of illness and was not admitted. Date of onset of empyema not known.

Discussion. In analyzing the pathologic findings in these hundred cases, the most striking observation is the absence of any specific gross or microscopic pathological lesion which, in the absence of additional clinical data, could lead to a diagnosis of measles. The most constant pathologic change appears to be pneumonia and inflammation of the upper respiratory tract, but even the pneumonia is not of a single type. Elsewhere the gross picture is one of secondary infection and concomitant toxic changes, the infection being most often apparently of a streptococcal nature. Microscopic examination also shows evidence chiefly of a severe and widespread toxic and infectious process. Among these changes, the frequent presence of an interstitial, mononuclear cell infiltration is of especial interest.

Brody and Smith,[1] in a study of the microscopic visceral pathology of a series of scarlet fever cases at this hospital, were particularly impressed by the repeated occurrence of an almost characteristic lesion found in various organs. This consisted of an interstitial round-cell infiltration (predominantly lymphocytic, but also containing plasma cells and other round cells). The infiltration tended to be perivascular in distribution, and practically never affected the specific structures of the organs, such as liver lobules or kidney glomeruli or tubules. They concluded that the process was most probably the result of a circulating streptococcus toxin, as the interstitial lesion is seen in other infectious diseases, notably diphtheria and measles, but always with an associated streptococcus infection.

This scarlet fever study constitutes a close parallel to our own, as in each the autopsies have been performed in the same laboratory and the microscopic sections prepared by the same routine. A similar purely interstitial mononuclear infiltration was observed in

the measles series in practically all of the 22 sections of the trachea, in 20 out of 89 liver sections, and in from 1 to 6 cases each in the heart, kidney, adrenal and pancreas. The 11 skin sections examined all showed slight mononuclear cell infiltration of the corium. Slight endothelial cell changes were observed in 4 of these, but in none were there the marked changes and proliferation of these cells described in measles rashes by Ewing,[4] Mallory and Medlar,[9] and Denton.[3]

The identity of the causative organism of measles does not lie within the province of this paper, but it is apparent that, in this series at least, the fatal complications of measles are due in very large part to the hemolytic streptococcus. This is evidenced by the bacteriologic studies described here, and also by the occurrence of the interstitial mononuclear infiltration and the correlation between this process and the observations cited in cases of scarlet fever, a known streptococcus disease. The large percentage of positive blood cultures at autopsy suggests that the blood stream is probably the chief route by which the organism is transmitted through the body, and the pharynx, tonsils and upper respiratory tract would seem a very likely portal of entry. This hypothesis is supported by the section of tonsil in which a blood-vessel passing through an area of acute inflammation underwent necrosis, with cocci seen passing from the inflammatory areas into the vessel.

Summary. 1. A series of 100 measles autopsies is presented, with gross and microscopic pathologic findings throughout the body, bacteriology, and various related clinical statistical data.

2. The incidence was greatest among small children, 60% of the cases falling between the ages of 6 and 24 months.

3. Pneumonia, laryngitis and encephalitis were early complications, while empyema occurred late in the disease. Death was usually in the second or third week.

4. Autopsy bacteriology studies showed hemolytic streptococcus, either alone or in combination with other bacteria, to be overwhelmingly the chief organism found.

5. No lesion definitely pathognomonic of measles was found. The most constant microscopic finding was an interstitial mononuclear cell infiltration, resembling a similar infiltrative process found extensively in scarlet fever.

In closing, I wish to express my appreciation and indebtedness to Dr. Vera B. Dolgopol, pathologist of Willard Parker Hospital, for her many helpful suggestions on the interpretation of findings.

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CONGENITAL POLYCYSTIC KIDNEY.

WITH REPORT OF ITS OCCURRENCE IN SEVERAL MEMBERS OF ONE FAMILY.

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HEREDITARY diseases, in most instances, offer certain stigma whereby they may be easily recognized. This is aptly illustrated in such hereditary afflictions as diabetes insipidus, hemophilia and others. On the other hand, in congenital polycystic kidney, it is often difficult to demonstrate any existing hereditary influence. It is by no means common, being found at postmortem in approximately 1 to 500 cases, and as such merits more than a passing interest.

This condition should be defined in contrast to other cystic conditions of the kidney, although the distinctions are not clear cut. A kidney in which there is a very great number of small cysts and larger cysts found throughout its parenchyma and projecting on its surface, both the cortex and the medulla being involved, is probably of congenital origin. The disease is not limited to any particular age, being found in fetuses, newborn, adults and even in old age. One often sees the statement in medical literature that polycystic kidney disease occurs in two periods of life, *viz*, early infancy and adult life, and furthermore, that there is a gap between these ages in which few cases occur. However, a search of the literature shows that a number of cases have been recorded occurring during the first and second decades. Sieber,[8] in 1901, collected 32 cases in these periods; the age recorded usually represented the time when the disease was first recognized, either clinically or postmortem. Several writers, studying families with hereditary polycystic kidney disease, have recognized cases in which no subjective symptoms have developed. Such facts bring the newborn and adult groups closer together; there is no longer any doubt that the disease in the adult and the infant are the same.

Theories of Development. Many theories have been advanced to explain the development of polycystic kidney disease and presented in far more detail than could be attempted in this paper. The most generally accepted theories are:

1. That of Hildebrandt,[5] who believes that the cysts are the outcome of a developmental defect, rather than inflammatory or neoplastic in character. The cysts, according to him, are formed as

a result of non-union of the collecting and secretory elements which arise from two separate anlagen.

2. That of Kampmeier,[6] who, as a result of extensive embryologic studies of congenital renal cysts, comes to the conclusion that during fetal life renal cystic tabules are very common, and as growth progresses, they disappear. However, if for some unknown reason they persist and continue to grow, polycystic kidneys result.

Heredity. The hereditary aspect has been widely commented upon. Examples occurring in families cannot be regarded as a coincidence, but only as proof that in these families, polycystic kidney disease is a hereditary affection. A familial history, therefore, is of the greatest diagnostic value. This recognition of several instances occurring in one family and in several successive generations is largely responsible for the term "congenital" now used with respect to this disease. The hereditary factor is not sex-linked; the disease affects either sex equally.

Dunger,[3] in 1904, was able to present 5 children of the same mother having polycystic kidney disease. Paus,[7] in 1914, found 2 of a family of 4 with cystic kidneys; 1 of those with cystic kidney had 14 children, of whom 4 had cystic kidneys. The other with cystic kidney had 3 children, none having the disease. One of the normal members of the first generation had 4 normal children, but a grandchild had a cystic kidney. Of more recent years, Cairns,[1] noted 10 cases in 3 generations of a family. Fuller,[4] in 1929, described 9 cases in 27 members of a family in 4 generations. While the application of Mendel's law to this condition has been suggested in the genealogic graphs published by authors, such as Cairns,[1] Crawford[2] and Fuller,[4] there is still insufficient data available to admit analysis along these lines.

The cases to be reported here are those of the T. family. Medically speaking, we can start the history of this family with 2 brothers, Mendel and Isaac T. A noteworthy incident from the outset is that the parents of the children in whom the disease was found are related, that is, the husband, Isaac T. and his wife, Bessie T., are also uncle and niece. Isaac T. died at the age of 42 of "chronic nephritis." We can find no evidence of any studies, either functional or urographic having been done on him.

Bessie T., the mother, has been suffering from renal disease for a number of years and has, on several occasions, passed renal sand. Recent urologic studies reveal impaired renal function, but no evidence of polycystic kidney disease.

Bessie and Isaac T. had 7 children. Of these, 6 give positive evidence of renal disease. Four of these 6 cases have both clinical and radiologic evidence of polycystic kidney disease.

Case Reports. Case 1.—Rose C., née T., aged 43, was admitted to this hospital on June 29, 1935, with the chief complaints of palpitation, nervousness and dyspnea, of 3 years' duration. Her past history is important in

that she suffered from nocturia for a number of years and was told that she had hypertension by a private physician. She passed a ureteral calculus in 1928.

Physical Examination. A fairly well nourished female with the following positive findings: Diseased tonsils; marked pulsations of vessels of the neck; soft systolic murmur at the mitral area not transmitted; in the upper left quadrant there was palpable a hard, rounded, pear-shaped mass which did not definitely move with respiration; the right kidney was palpable; there was a fine tremor of the fingers.

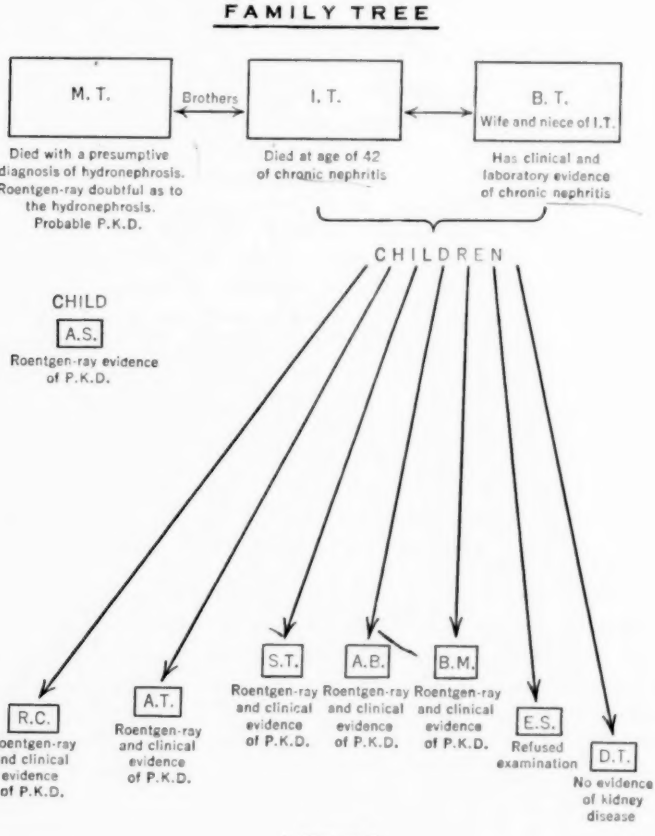

CHART I

Laboratory Studies. Temperature, 98.4; pulse, 80 to 95; respiration, 20. *Urine*, straw colored, acid, specific gravity, 1.016; faint trace of albumin, 2 to 3 leukocytes, occasional red blood cells, hyaline and coarsely granular cysts. *Leukocytes.* 11,400. *Urea-nitrogen*, 15.5; *Sugar*, 94; *Cholesterol*, 224. *Mosenthal Test:* impaired kidney function. *Electrocardiogram:* myocardial degeneration. *B.M.R*, +35, +51, +28. *Urography:* Roentgen ray of right kidney showed marked dilatation of the renal pelvis; left kidney enormous dilatation of all calices. Administration of Lugol's solution caused swelling of the thyroid gland and no improvement of symptoms.

Therefore, it was not thought that this patient suffered from primary hyperthyroidism.

Diagnosis. 1, bilateral polycystic kidneys; 2, hypertensive cardiovascular disease with hypermetabolism; 3, foci of infection. Patient discharged on July 19, 1935.

CASE 2.—Herman T., aged 36, was admitted on December 6, 1935, with chief complaints of pain in the left loin, and hematuria.

History of Past Illness. Two weeks prior to admission, patient began to develop sharp non-radiating pain in the left loin. He also noticed that his urine was reddish in color, having been so for the past 6 months. There were no other urinary symptoms, and the patient was in general good health. There was a past history of scarlet fever.

Physical Examination. A well-nourished intelligent white male. The positive findings were injected pharynx; diseased tonsils; a mass on the left side of the abdomen, in the region of the kidney, which moved with respirations. There was no tenderness nor rigidity.

Laboratory Studies. Temperature, normal. Pulse, 80; respiration, 20. *Urine*, amber, acid, cloudy, specific gravity, 1.011; faint trace of protein, 22 to 25 leukocytes, blood, occasional casts. *Blood*, mild leukocytosis, 10,900. *Blood-chemistry*, normal. *Wassermann test*, negative. *Indigo carmine*, right appeared in 8 minutes; left in 9. *Roentgen ray*, retrograde pyelogram revealed the pelvices markedly dilated and distended. There were stone shadows on the left side.

Diagnosis. Congenital polycystic kidneys with stones.

CASE 3.—Samuel T., aged 35, was admitted to the hospital on December 19, 1935, with the chief complaints of dyspnea and expectoration. He presented a history of marked asthmatic attacks of 20 years' duration.

Past History. Marked myopia since childhood. Hematuria and loin pain of 1 week's duration in 1934. At present he occasionally suffers from attacks of loin pain, frequency of urination and nocturia.

Physical Examination. Revealed dyspnea; cyanosis of lips; curvature of finger nails; marked myopia; impaired percussion at both bases; bronchovesicular breath sounds in same area; sibilant sonorous râles heard throughout, and subcrepitant râles in the bases. The heart was negative. The abdomen showed diastasis recti, tenderness in the right loin space, and a palpable right kidney.

Laboratory Studies. Urine, straw colored, cloudy, specific gravity, 1.020, faint trace of protein, 1 to 2 leukocytes, frank blood, occasional hyaline and granular casts. *Cystoscopic urine*, right kidney, 10 to 60 red blood cells, occasional leukocytes, acid, cloudy. Left kidney, 5 to 8 red blood cells, occasional leukocytes. *Indigo carmine*, right appeared in 4 minutes; left, in 10. *Blood count*, normal. *Roentgen-ray*, retrograde pyelography revealed both kidneys larger than normal. The calices clubbed, dilated, and the upper ones enlarged.

Diagnosis. 1, Polycystic kidney; 2, bronchitis with bronchiectasis; 3, marked myopia.

CASE 4.—Anna B., née T., aged 35, has complained of fatigue and a dull pain in the lumbar region for the past 8 months. She has no urinary complaints.

Physical Examination. A slightly obese female with the following positive findings: Diseased tonsils; slight cardiac enlargement in the region of the left ventricle; a faint systolic murmur; accentuated second aortic sound; blood pressure, 160/98; fullness in the right upper and mid-abdominal quadrants.

Laboratory Studies. Urine, negative except for a faint trace of protein. Specific gravity, 1.018. *Intravenous urography*, revealed extensive bilateral polycystic kidneys.

Diagnosis. 1, Bilateral polycystic kidney disease; 2, foci of infection.

Case 5.—Belle M., née T., was admitted to another hospital in 1929 for study because of recurrent right loin pain, frequency and nocturia.

Physical Examination. Negative except for palpable lower lobe of left kidney, and marked enlargement of right kidney.

Laboratory Studies. Catheterized urine, revealed pus. *Indigo carmine,* right appeared in 5 minutes; left, in 6. *Roentgen ray,* pelvis and calices of both kidneys were enlarged. Marked deformity of the right kidney.

Diagnosis. Probable right-sided pyonephrosis. In 1930, the patient was admitted to the Atlantic City Hospital in a coma. She died within 2 hours, and a diagnosis of uremia with chronic nephritis was made. The original Roentgen ray plates have been destroyed, but this patient undoubtedly was suffering from the same affliction as other members of her family, with a superimposed pyogenic infection on the right side.

Case 6.—Edith S., née T., is at the present time being treated by her family physician for kidney disease. A flat plate of the abdomen was taken 2 years ago and was found to be negative. She refused to permit further urologic studies to determine the presence or absence of polycystic kidney disease.

Case 7.—David T., aged 25, is apparently free of renal disease. He presents no urinary symptoms nor signs, and there is no Roentgen ray evidence of diseased kidneys.

Case 8.—Mendel, the brother of Isaac, first presented symptoms of renal disease in 1909 when he visited a physician because of recurrent attacks of hematuria and loin pain. This continued intermittently until 1919 when both kidneys became definitely palpable upon manual examination. In 1921, urographic studies revealed an irregular abnormal shadow in the left kidney region extending down to the crest of the ilium. The roentgenologist was unable to make a definite diagnosis. His interpretation was that it might either be due to a tuberculous kidney or a hypernephroma. Mendel T. continued to have hematuria, obliguria, and passage of sand, and died in 1924 with a presumptive diagnosis of hydronephrosis. In the light of the family history, it is fair to assume that Mendel also suffered from polycystic kidney disease.

Case 9.—Mrs. S., a daughter of Mendel T., was recently in the hospital with complaints referable to the renal system. Roentgen ray evidence revealed beginning kidney lesions, *viz.*, dilatation of calices and pelvis.

Clinical Course and Diagnosis. The majority of symptoms in polycystic kidney disease are due to renal insufficiency, a definite impairment of function being demonstrable in about two-fifths of the patients when they first consult a physician. In a typical case one obtains symptoms and signs of loin pain, hematuria, nocturia, frequency, loss of weight, unilateral or bilateral masses in the loin, hypertension, a systolic pressure of 150 mg. Hg. or higher being found in 50% of the adults with clinical symptoms, and the percentage with hypertension is still higher in the group with marked renal insufficiency. The persistent presence of hypertension in these cases is attributed to a generalized vascular disturbance as shown by the high incidence of renal sclerosis, and to the finding of obliterative changes in the arterioles and small arteries of the kidney. Whether the vascular sclerosis, especially in the kidney, is the primary factor, and the hypertension and renal functional disturbances secondary, is a moot point. The functional disturbances are similar to those found in patients with contracted kidneys. There is decreased

elimination of phenolsulphonephthalein, retention of nitrogenous substances in the blood, and a decreased ability to concentrate the urine. Death is usually due primarily to renal insufficiency unless one of the kidneys becomes infected.

While postmortem examinations show that in many instances the polycystic kidney is not suspected in life, death being due to other causes, there are certain diagnostic and investigative procedures which serve to prove the presence of the disease.

The two most important aids to diagnosis are: a family history and the pyelogram. Very often, this latter study is the one means of making a differential diagnosis from such conditions as hydronephrosis and neoplastic lesions of the kidney.

Treatment. Almost all who have studied this condition are in accord with the statement that conservatism in treatment is the method of choice. Surgery carries a high mortality. The same medical treatment as is given to any nephropathy, irrespective of its cause, is used. Where infection complicates the picture, drainage and pelvic lavage often help.

Summary. 1. Polycystic kidneys in 9 members of one family are reported. 2. The importance of a careful family history and pyelographic examination as the two most important factors for such a diagnosis are stressed.

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BOOK REVIEWS AND NOTICES.

A Woman Surgeon. The Life and Work of Rosalie Slaughter Morton. Foreword by Dr. Hugh Hampton of Johns Hopkins. Pp. 399; 1 illustration. New York: Frederick A. Stokes Company, 1937. Price, $3.00.

Here is a story to encourage the faint-hearted and to justify the superiority complex that is coupled with a compelling desire to work helpfully. Overcoming the handicaps of poverty and the family and the public opposition of the 90's to a woman in medicine, this buoyant young lady, before she was 25, had graduated from the Women's Medical College of Philadelphia, completed an internship, studied at Göttingen and Vienna (securing special favors from the leading teachers), visited Russia with the Ehrlichs, penetrated to Tolstoi's friendship, broken down Ibsen's barriers and done experiments with Horsley. It was unnecessary for her to tell us that her philosophy of life was one of action. What matter that the by-gone German words are often misspelled, and that all turns out for the best in these gilded pages? One who founded the American Women's Hospitals, was 9 times decorated for distinguished war service and who aided 60 Serbian students to an American education, can well be pardoned some poetic license when it comes to attributing all "crossness" to ill-health or announcing that the electrochemical changes of toxemia and "a chain of other pathologies" are now generally recognized, or maintaining that intelligent information and coöperation is all that is needed to obliterate disease from the earth.

This is an interesting story, well told. The bed light is turned off each night with regret, and few will not be eager to carry through to the end. Especially by the women of our profession will this autobiography be cherished.

E. K.

The Fundamentals of Electrocardiographic Interpretation. By J. Bailey Carter, M.D., Clinical Instructor, Department of Medicine, Rush Medical College, the University of Chicago; Associate Staff, Cook County and Augustana Hospitals, Chicago. With a Foreword by Horatio Burt Williams, M.D., Dalton Professor of Physiology, College of Physicians and Surgeons, Columbia University, New York. Pp. 326; 250 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $4.50.

To the number of good, concise, accurate books on electrocardiography and its clinical interpretation can now be added this one from Chicago. It not only has the advantage of being the latest in a still rapidly changing field, but has certain special features of advantage: an 8-page glossary for those not experienced in the specialty, and 75 pages of a bibliography of the literature of the past 20 years (classified in an alphabetical list of subjects such as acids, aconite, action currents, etc.) for those who wish to delve further. The illustrations are good and numerous, and a proper emphasis has been placed on the limitations of the method.

E. K.

AN INTRODUCTION TO COMPARATIVE BIOCHEMISTRY. By ERNEST BALDWIN, B.A., PH.D., Fellow of St. John's College, Cambridge; University Demonstrator in Biochemistry, Cambridge. With a Foreword by PROF. SIR FREDERICK GOWLAND HOPKINS, F.R.S. Pp. 112; 11 illustrations and 9 tables. New York: The Macmillan Company, 1937. Price, $1.50.

HEREIN is presented, in a clear and logical manner, concepts of fundamental chemical adaptations, exercise of which has permitted the animal organism to function in progressively varying environments. The significance of the ionic composition of blood, which varies little from sea water and only slight variations of which are tolerated; the concept of the complex organs of man and the higher animals in terms of their biologic past, but more particularly in terms of maintenance of a stable environment against a varying external one (animal forms have resorted to semipermeable membranes and essential water-excreting mechanisms, waterproof coverings such as chitin or slime, chloride-secreting cells in the marine fish, urea-impermeable cells in marine elasmobranchs and various types of kidneys); the combat of ammonia intoxication which begins with decreased water supply; the adjustment to a non-aqueous oxygen supply by morphologic and chemical means—these are some of the problems the author presents. Morphologic and chemical data are interrelated in such a way as to give the reader information and a basis for interpretation of such study.

O. H.

HEART DISEASE. By PAUL DUDLEY WHITE, M.D., Lecturer in Medicine, Harvard Medical School; Physician to the Massachusetts General Hospital, Boston. Pp. 744; 125 illustrations. Second edition, completely rewritten and reset. New York: The Macmillan Company, 1937, Price, $7.50.

Two valuable appendices have been added to this edition: one, giving a chronologic outline of the evolution of knowledge of heart disease; the other, a list of names recommended for cardiac diagnoses by the American Heart Association. Unfortunately, however, this is counterbalanced by a considerable reduction in the bibliography, and in that part that deals with methods of examination. Otherwise, the merits of the first edition are continued in the second.

E. K.

THE MEDICAL CLINICS OF NORTH AMERICA, VOL. 21, NO. 1 (Chicago Number, January, 1937). Pp. 330; illustrated. Philadelphia: W. B. Saunders Company, 1937.

FIVE papers on Diseases of Metabolism and three on allergy contribute about one-third of this volume, the other articles being distributed over a wide range. Whether or not due to an effort to be "practical," too many of these articles exhibit an unfortunate amount of dogmatism, unproved assertion and even fallacious reasoning.

E. K.

CARCINOMA OF THE FEMALE GENITAL ORGANS. By M. C. MALINOWSKY and E. QUATER. Translated from the Russian by A. S. SCHWARTZMANN, A.B., M.D. Pp. 255; 50 illustrations (3 in colors). Boston: Bruce Humphries, Inc., 1936. Price, $5.00.

THIS is a discussion of cancer of the female genitalia, including the breast, presented by 9 collaborators in addition to the named authors. There is a distinct emphasis on pathology and especially noteworthy is the discussion on Krukenberg tumors of the ovary, which includes original anatomic studies on the lymphatic connection between the stomach and the ovaries. The references are almost entirely from Russian and German sources and hence it is striking that no reference has been made to the use of the colpo-

scope and the Schiller test in the diagnosis of cervical cancer. The Reviewer was happy to note that Clark of Philadelphia was properly given credit for having performed the first so-called "Wertheim" operation. The omission of any mention of the rarer ovarian malignancies such as arrhenoblastoma and granulosa cell tumor is an important defect in a work of this nature, while the lack of any index and an extremely poor bibliography detracts from the value of the book. F. B.

FAVOURITE PRESCRIPTIONS. (The Practitioner Handbooks.) Edited by SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., F.R.C.P., and ALAN A. MONCRIEFF, M.D., F.R.C.P. Pp. 227. London: Eyre & Spottiswoode, Ltd., 1936. Price, 10/6.

THIS little handbook, the first of a series of such works to be issued in conjunction with "The Practitioner," contains 18 chapters describing the pharmacopœias of 11 large general hospitals and 6 special hospitals of London, Edinburgh and Dublin and the National Formulary for National Health Insurance. There are cited numerous prescriptions which experience has shown to be valuable, and many of which have a historical interest. The Reviewer quotes a few significant sentences: "A function of a hospital pharmacopœia is to simplify the work of the dispensary and to economize in drugs and effort. To the student and young practitioner it also serves as a guide and sometimes as an inspiration;" "The newly qualified practitioner needs help in the art of prescribing, and his own hospital pharmacopœia should provide that help. . . . Surely the craftsman should know his tools and how to use them with energy and skill;" "Fashion in prescribing and in treatment is still a large factor in the choice of drugs;" "In prescribing the potent drugs, physicians tend to use less and less stock mixtures of their hospital formulary, and order instead the active principle uncombined." The physician will find here much that is interesting and useful. R. K.

INHALATION ANESTHESIA. A Fundamental Guide. By ARTHUR E. GUEDEL, M.D., Associate Clinical Professor of Surgery (Anesthesia), University of Southern California School of Medicine. Pp. 172; 6 charts. New York: The Macmillan Company, 1937. Price, $2.50.

THIS book has been prepared by the author with the aid of Drs. Walter Meek, Ralph Waters, Chauncey D. Leake, Peter K. Knoefel, Clinton Thienes and Douglas Drury. In the first of the two parts, there is a full discussion of inhalation anesthesia, in which the mechanism of anesthetic action, the stages and signs of anesthesia and its depths are concisely described. In addition, there is a chapter on the preparation of the patient and the selection of the anesthetic agent. The second part of the book deals with anesthetic accidents. Changes in blood pressure, ventricular fibrillation, respiratory failure, cyanosis, etc., are discussed. The last two chapters deal with the prevention of anesthetic explosions. A list of selected references is appended.

The book is an admirable one. It is prepared so that a beginner in anesthesia may easily and rapidly become acquainted with the principles of anesthetic administration. The author has stressed the physiology of anesthesia, both in the discussion of the administration of anesthesia and in pointing out the cause and prophylaxis of anesthetic accidents. Throughout the text illustrative reports of cases are inserted.

The book should be in the hands of every anesthetist and is recommended especially to beginners in the field. L. F.

THE TRUE PHYSICIAN. The Modern "Doctor of the Old School." By WINGATE M. JOHNSON, M.D. Pp. 157. New York: The Macmillan Company, 1936. Price, $1.75.

THERE has been considerable agitation in the past decade about the changing order in medicine; while the passing of the old-fashioned doctor has been lamented for a much longer period. One good result of this agitation has been to make it increasingly apparent that a modern type of "the doctor of the old school" has unobtrusively been emerging. The family doctor, with his trials and triumphs, professional hardships and consolations, is once more being recognized as the cornerstone of our profession. In fact, he always has been so recognized by the discerning.

This little book will tell in simple terms what the young man who is thinking of taking up medicine or the medical student or intern would like to know from one who has been through the mill. One who obviously has his fair share of the milk of human kindness not only gives out practical information of considerable value to the neophyte; but also, and more important, conveys an atmosphere of reasonable optimism that should help us all on our way toward acquiring "the true philosophy of life."

E. K.

VASCULAR DISORDERS OF THE LIMBS. Described for Practitioners and Students. By SIR THOMAS LEWIS, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician in Charge of Department of Clinical Research, University College Hospital, London; Consulting Physician, City of London Hospital, etc. Pp. 111; 5 illustrations. New York: The Macmillan Company, 1936. Price, $2.00.

THIS booklet may be regarded as outlining for the practitioner the results of the distinguished author's studies of the peripheral vascular diseases, somewhat as his earlier booklets on the heart followed his cardiac investigations that were so well presented in his "Mechanism of the Heart Beat." The 10 chapters cover: "The Circulation in the Limb and Its Testing;" "Effects of Circulatory Arrest;" "Embolism and Thrombosis of Main Arteries;" "Post-Ischæmic Contracture, Intermittent Claudication;" "Arteriosclerosis, Thrombo-angiitis Obliterans;" "Vasoconstriction, Local Arterial Spasms;" "Spasmodic Arterial Obstruction, Raynaud's Phenomenon;" "Gangrene (Bilateral Forms, Cervical Rib, General);" "Vasodilatation, Flushing;" "Vascular Disorders in Diseases of the Nervous System." The relatively low price makes it easy for the progressive physician to add to his medical library this authoritative statement by one who has himself added so much to our increased knowledge of disorders of the peripheral circulation.

E. K.

APPLIED DIETETICS. The Planning and Teaching of Normal and Therapeutic Diets. By FRANCES STERN, Chief of Food Clinic, The Boston Dispensary; Assistant in Medicine, Tufts College Medical School, etc. Pp. 263; many tables and charts. Baltimore: The Williams & Wilkins Company, 1936. Price, $3.50.

EIGHTEEN years of experience in the Food Clinic of the Boston Dispensary (the first clinic of its kind in the country) in fulfilling the food prescription given by the physician, in the guidance of patients, in the instruction of students, dietitians, social service workers, nurses and physicians, furnish the background and material for this highly practical volume. Fifty-two tables simplify the computation of diets. The book is recommended to all students and physicians.

R. K.

AMINO ACID AND AMMONIA METABOLISM IN LIVER DISEASES. By ESBEN KIRK. Pp. 147. Copenhagen: Levin & Munksgaard, 1936. Price Dan. Kr. 10.

IN his thesis for the doctorate in medicine, the author presents observations in normals and in patients with liver disease, and also experimental data on the rôle of the liver in amino acid and ammonia metabolism. It is generally agreed that the liver is the exclusive site of urea formation in the body and is also chiefly responsible for the deaminization of the amino acids. The reserve of the liver in regard to both of these functions is very great, as little as one-fifth of the liver tissue being able to carry on. Thus the author failed to find any difference between normals and patients with liver disease (acute hepatitis, cirrhoses, obstructive jaundice) in the plasma amino nitrogen concentration or the amino nitrogen excretion during fasting and after glycine administration. The finding of increased blood ammonia values in liver cirrhosis is not to be explained as due to impaired urea synthesis in the liver, but, as the author shows, may be correlated with the existence in cirrhosis of a collateral circulation permitting ammonia absorbed from the intestines to avoid the liver and empty directly into the vena cava. R. K.

CLINICAL LABORATORY DIAGNOSIS. By SAMUEL A. LEVINSON, M.S., M.D., Director of Laboratories, Research and Educational Hospitals, Chicago; Associate Professor of Pathology and Bacteriology and Assistant Professor of Medicine, University of Illinois College of Medicine, and ROBERT P. MACFATE, CH.E., M.S., Assistant Director of Laboratories, Research and Educational Hospitals, Chicago; Associate in Pathology and Bacteriology and Instructor of Physiological Chemistry, University of Illinois College of Medicine. Pp. 877; 144 illustrations; 13 plates (5 in colors) and 78 tables. Philadelphia: Lea & Febiger, 1937. Price, $9.50.

"THIS book is unique among texts in its field in that it offers not only a satisfactory review of clinical laboratory diagnosis but presents special chapters on laboratory procedures in legal medicine and toxicology, in pediatrics and in similar subjects not usually included in a book of this character. It provides a rapid review of the entire field, correlating the didactic subjects with clinical diagnosis. The technique for obtaining and examining the various materials is given and the pathologic findings are compared with the normal. Brief reviews of anatomy, physiology, biochemistry and of the outstanding diseases aid the intern and the practicing physician in the study of those cases requiring laboratory methods. . . . The system of hematology and the histologic technique employed are those of Dr. R. H. Jaffé, of the Cook County Hospital in Chicago. The chapter on Pediatric Procedures is contributed by Dr. H. G. Poncher, of the University of Illinois, College of Medicine, while the technique for the toxicologic examination of materials is that formulated by Dr. C. W. Muehlberger, Coroner's Toxicologist, Cook County, Illinois." (Publisher's statement.)

NEW BOOKS.

Diagnosis and Non-operative Treatment of the Diseases of the Colon and Rectum. By GOTTWALD SCHWARZ, M.D., Professor, University of Vienna; Head *X*-ray Department, Kaiserin Elizabeth Hospital, Vienna, JACQUES GOLDBERGER, M.D., Consulting Physician, Carlsbad, and CHARLES CROCKER, M.D., New York, N. Y. Pp. 540; 246 illustrations and 9 colored plates. New York: Paul B. Hoeber, Inc., 1937. Price, $10.50.

Autonomic Neuro-effector Systems. (Experimental Biology Monographs.) By WALTER B. CANNON, George Higginson Professor of Physiology, Harvard University, and ARTURO ROSENBLUETH, Assistant Professor of Physiology, Harvard University. Pp. 229; 42 illustrations. New York: The Macmillan Company, 1937. Price, $4.00.

Epidemiologie. Grundbegriffe und Ergebnisse. By PROF. DR. MED. ADOLF GOTTSTEIN, Ministerial-Direktor i. R., Berlin. Pp. 285; 16 illustrations. Wien: Franz Deuticke, 1937. Price, Paper, M. 15; Bound, M. 17.40.

Pression Solaire Faisceau Energétique et Biologie. Biogenèse et Pathogenèse. By DOCTEUR G. FROIN, Ancien Interne des Hôpitaux de Paris. Pp. 327; 38 illustrations. Paris: Librairie Girardot et Cie, 1937. No price given.

The British Encyclopædia of Medical Practice. Volume 3. Cataract to Diaphragm Diseases. Under the General Editorship of SIR HUMPHRY ROLLESTON, BT., G.C.V.O., K.C.B., M.D., D.Sc., D.C.L., LL.D., Emeritus Regius Professor of Physic, Cambridge, etc. With the assistance in a consultative capacity of F. R. FRASER, M.D., F.R.C.P.; G. GREY TURNER, D.Ch., M.S., F.R.C.S.; JAMES YOUNG, D.S.O., M.D., F.R.C.S. Ed., F.C.O.G.; SIR LEONARD ROGERS, K.C.S.I., M.D., LL.D., F.R.C.P., F.R.C.S., F.R.S., and F.M.R. WALSHE, O.B.E., M.D., D.Sc., F.R.C.P. Pp. 735; 77 illustrations and 12 plates (8 in color). London: Butterworth & Co. (Publishers) Ltd., 1937. Price, $12 per volume.

This volume covers some 60 odd articles from "Cataract" to "Diaphragm Diseases"—none of outstanding length. The reader is referred to this Journal (**193**, 711, 1937) for a consideration of the earlier volumes.

Personality and the Cultural Pattern. By JAMES S. PLANT, M.D., Director, Essex County Juvenile Clinic. Pp. 432. New York: The Commonwealth Fund, 1937. Price, $2.50.

Pediatric Dietetics. By N. THOMAS SAXL, M.D., F.A.C.P., F.A.A.P., Associate and Lecturer in Diseases in Children, New York Post-Graduate Medical School, Columbia University; Assistant Attending Physician, Babies' Ward, New York Post-Graduate Hospital, etc. Foreword by ADOLPH G. DE SANCTIS, M.D., F.A.A.P., Director of Pediatrics at the New York Post-Graduate Medical School and Hospital, Columbia University. Pp. 565; 57 illustrations and 2 colored plates. Philadelphia: Lea & Febiger, 1937. Price, $7.00.

Annual Report of the Indian Institute for Medical Research 1935–1936. Issued by the Governing Body. Pp. 84. Calcutta: Indian Institute for Medical Research, n.d.

Maternal Care. The Principles of Antepartum, Intrapartum, and Postpartum Care for the Practitioner of Obstetrics. Approved by The American Committee on Maternal Welfare, Inc., Prepared by DRS. W. C. DANFORTH, G. W. KOSMAK, R. L. DENORMANDIE, F. L. ADAIR. F. L. ADAIR, Editor. Pp. 93. Chicago: The University of Chicago Press, 1937. Price, $1.00.

The Biology of Human Conflict. An Anatomy of Behavior, Individual and Social. By TRIANT BURROW, M.D., PH.D., Scientific Director, The Lifwynn Foundation, New York City. Pp. 435. New York: The Macmillan Company, 1937. Price, $3.50.

Papers from the IV Medical Service of St. Erik's Hospital, Stockholm. Edited by HILDING BERGLUND. Pp. 269; illustrated. Stockholm: Alb. Bonniers Boktryckeri, 1937.

League of Nations. Bulletin of the Health Organization. Vol. VI, No. 1 (February, 1937). Edited by Health Section of the League of Nations, Geneva. Pp. 127; 24 illustrations. New York: Columbia University Press, 1937. Price, 65c.

The Medical Clinics of North America, Vol. 21, No. 3 (Mayo Clinic Number, May, 1937). Pp. 956; illustrated. Philadelphia: W. B. Saunders Company, 1937.

This number contains 21 articles, including a symposium on gastro-intestinal diseases by A. B. Rivers and L. A. Carlson (Some Extragastric Causes of Dyspepsia); J. F. Weir (Pancreatitis); P. W. Brown (Constipation); J. A. Bargen (The Treatment of Diarrhea); E. G. Wakefield ("Spastic Colitis;" Functional Disorder of the Colon Affecting Young and Middle-aged Individuals); D. L. Wilbur (Vitamin Deficiency Diseases: Their Diagnosis and Treatment).

Infantile Paralysis and Cerebral Diplegia. Methods Used for the Restoration of Function. By ELIZABETH KENNY. With a Foreword by HERBERT J. WILKINSON, Professor of Anatomy and Dean of the Faculty of Medicine, University of Queensland. Pp. 125; 51 illustrations. Australia: Angus & Robertson Limited, 1937. Price, £1/1/-.

International Clinics. Vol. II. Forty-seventh Series, 1937. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 13 Collaborators. Pp. 315; many illustrations, 1 in color. Philadelphia: J. B. Lippincott Company, 1937.

The usual wide range of subjects is covered in this volume entirely by American writers.

Twins. A Study of Heredity and Environment. By HORATIO H. NEWMAN, FRANK N. FREEMAN, KARL J. HOLZINGER. Pp. 369; 33 figures, 39 plates of illustrations and 96 tables. Chicago: The University of Chicago Press, 1937. Price, $4.00.

NEW EDITIONS.

The Treatment of Diabetes Mellitus. By ELLIOTT P. JOSLIN, M.D. (HARVARD), M.A. (YALE), Medical Director, George F. Baker Clinic, New England Deaconess Hospital; Clinical Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital. With the Coöperation of HOWARD F. ROOT, M.D., Physician, New England Deaconess Hospital; Instructor in Medicine, Harvard Medical School, PRISCILLA WHITE, M.D., Physician, New England Deaconess Hospital; Instructor in Pediatrics, Tufts College Medical School, ALEXANDER MARBLE, M.D., Physician, New England Deaconess Hospital; Assistant in Medicine, Harvard Medical School. Pp. 707; 22 illustrations and 142 tables. Sixth edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $7.00.

Surgical Anatomy. By GRANT MASSIE, M.B., M.S. (LOND.), F.R.C.S. (ENG.), Assistant Surgeon, Guy's Hospital; Lecturer in Operative Surgery, Guy's Hospital Medical School. Pp. 468; 153 illustrations, many in color. Third edition. Philadelphia: Lea & Febiger, 1937. Price, $6.50.

"Since the last edition of this book appeared yet another change in anatomical nomenclature has come about, and the situation from the viewpoint of the teacher of surgery is even more confused. In these circumstances it has appeared to the author that the purpose of this book is best served by retaining the old nomenclature, giving as hitherto the B.N.A. in brackets, and by making use of such terms descriptive of position as medial and lateral, which are so obviously better. . . . The text has been carefully revised and various additions and alterations have been made. As hitherto, every effort has been made to strike a balance between the anatomical and surgical matter. The number of illustrations has also been augmented." (From author's Preface.) (For reviews of previous editions, see this Journal **176**, 727, 1928; **187**, 412, 1934.)

The Morphine Habit and Its Painless Treatment. By G. LAUGHTON SCOTT, M.R.C.S., B.A. (OXON.), Late Senior Physician, London Neurological Clinic; Late Chief Assistant, Neurological Department, Guy's Hospital. Pp. 105. Second edition. London: H. K. Lewis & Co., Ltd., 1937. Price, 5s.

The Alimentary Factor in Disease. By MAX. H. KUCZYNSKI, M.D., D.Sc., Pathologist to the Ministry of Public Health of Peru; Professor of Physiopathology at the University of San Marcos, Lima, Peru, etc. Pp. 130. Second edition of "Studies on Nutrition." The Hague: G. Naeff, 1937. Price, 3 Guilders.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
JOHN H. MUSSER
PROFESSOR OF MEDICINE, TULANE UNIVERSITY OF LOUISIANA, NEW ORLEANS.

SOME CLINICAL ASPECTS OF CERTAIN BACTERIAL DISEASES.

THE application of the routine use of blood cultures to patients with fever of undetermined etiology often leads to surprising results in the establishment of a diagnosis. One cannot overemphasize the importance of this procedure not only in long continued fevers but in febrile states of short duration as well. In addition to the usual cultural methods, the inclusion of an anaërobic technique is necessary to complete the worth of this diagnostic aid. The bacteroides group demonstrates the wisdom of such thoroughness.

Bacteroides Infection. Much interest has been aroused in the continental literature, particularly in France, in bacteroides and related infections. Few reports have reached the English literature, but those which have, demonstrate clearly that a more widespread recognition of these infections probably awaits an increased interest in them rather than an increased frequency of occurrence.

While described in Europe and the United States as early as the turn of the century,[14] it was not until 1919 that Castellani and Chalmers[9] brought under the term *bacteroides* the large group of non-spore-forming obligative anaërobic bacilli. Certain Gram-positive anaërobic cocci cause similar symptoms as well and must be kept in mind in a discussion of this group. While these anaërobes are specifically distinct from one another[34] they have in common the characteristic of living as saprophytes in the natural cavities of the human body, the mouth, pharynx, intestine and genito-urinary tract. Most important of this group clinically has been *Bacteroides funduliformis*, particularly in Parisian infections.[34] For an adequate consideration of the bacteriological aspects the reader is referred to the paper of Henthorne, Thompson and Beaver.[22]

Thompson and Beaver[50] in 1932 found 10 reported cases due to *Bacteroides fragilis* and *Bacteroides funduliformis*. None were in the English literature. They reported 2 cases with organisms isolated from the blood by an anaërobic technique. Both patients had lesions in the genito-urinary tract, one prostatic hypertrophy, the other carcinoma of the bladder. In both these patients the disease was not a primary one, serious pathologic states being present and paving the

way for this most serious complication. Both patients developed infected pulmonary emboli with septic infarction. Cohen[11] has reported *Bacteroides funduliformis* in lung abscess and Beaver, Henthorne and Macy[5] in sepsis with hepatic abscess. Dixon and Deuterman[14] have more recently added 5 new cases.

Lemierre's[34] description of the clinical features of these septicemias is clear and complete. From the sites where these organisms live as saprophytes, that is, in the mouth, tonsils, middle ear, mastoid, appendix, puerperal uterus and urinary tract, during an inflammatory process these organisms, commonly *Bacteroides funduliformis*, find their way to the blood stream where infected emboli are released. Regardless of origin there are certain clinical characteristics common to the group, producing a syndrome "so characteristic that it permits of diagnosis before bacteriologic examination, including blood culture, has provided conclusive proof." He further points out that the postanginal septicemia, described as due to *Bacteroides funduliformis*, has the same general features as the septicemia ascribed in the older German literature to *Bacillus symbiophiles* and that *Fusobacterium nucleatum*[18a] isolated in several cases in Zurich is identical with *Bacteroides funduliformis*. Although symptoms depend largely on the organs involved, the symptomatic triad, high fever, pulmonary infarcts, and suppurative arthritis, is commonly present. Dixon and Deuterman found the liver affected in most cases and jaundice, varying from moderate to extreme, occurred 4 to 7 days after the onset of infection. Lemierre found jaundice less constantly, but considers it highly significant when present. Septicemia in otitis media has followed suppurative thrombophlebitis of the cavernous sinus. In posttonsillitis cases, as well, venous thrombosis seems to be a link between the tonsillitis and the generalized infection.[18b] Autopsy on such cases has shown peritonsillar thrombophlebitis and accounts for the procedure of internal jugular ligation as a therapeutic measure.

Dixon and Deuterman's 5 postoperative cases occurred in patients from 35 to 64 years of age and symptoms of bacteremia began 10 to 18 days postoperatively, interrupting an uneventful convalescence with a chill and sudden elevation of temperature, followed by daily chills and temperature to 106° F. They describe profuse perspiration as a distinctive feature. Five to 7 days may elapse following development of symptoms until blood cultures become positive.

Lemierre's[34] patients were mostly adolescents or young adults of either sex with either an inadequately drained tonsillar or peritonsillar abscess or deep-seated tonsillitis. In those in whom the syndrome develops 4 to 5 days following the onset of local inflammation, a true chill and high fever occur. At times the symptoms do not develop until as late as 12 days, sufficient time elapsing for the initial fever to have disappeared. Cervical adenopathy is present. All such infections seen by Lemierre have not been pure septicemias. All have been accompanied by the formation of distant metastatic abscesses, particularly in the lungs, even as early as the first day. These lesions start as septic infarcts with pain and dyspnea, and even blood stained sputum, a pleural friction rub and râles. Empyema has occurred. Joint lesions are very frequent, ranging from simple pains to suppurative arthritis, particularly in the shoulders, elbows, knees, sternoclavicular or sacro-

iliac articulations. Icterus has already been mentioned. Suppuration elsewhere may occur, for example, in the peritoneal cavity and psoas muscle. There is usually a leukocytosis and, in chronic cases, an anemia.

The course of the disease varies. Rapid and fatal termination in 7 to 15 days may occur. Such patients have continuously high fever, prostration, and die in coma. The disease may last 3 to 6 weeks with irregular fever ending in cachexia and delirium. An extremely grave prognosis accompanies the condition. Of 20 cases observed by Lemierre only 2 recovered. Dixon and Deuterman's mortality was 83%.

Lemierre states "to anyone instructed as to the nature of these septicemias it becomes relatively easy to make a diagnosis on the simple clinical findings. The appearance and repetition several days after the onset of a sore throat (and particularly of a tonsillar abscess) of severe pyrexial attacks with an initial rigor, or still more certainly, the occurrence of pulmonary infarcts and arthritic manifestations, constitute a syndrome so characteristic that mistake is almost impossible." Final diagnosis, of course, rests on bacteriologic ground—smears, cultures, and animal injections.

Treatment is purely supportive. No specific therapy is known. Antiseptic dyes have been used intravenously but with poor results.

Pyocyaneus Infection. Recent years have produced the recognition of a number of clinical pictures caused by commonly known organisms but not generally associated with the usual expressions of infection with these bacteria. *B. pyocyaneus* is one of these organisms. A well known pyogen, it is widely distributed in nature and usually considered a secondary invader of low virulence. Most characteristic of its growth is the production, in the presence of abundant oxygen, of a bright bluish-green fluorescence. It usually lives in saprophytic contentment in the normal mouth, skin and intestines of man; but at times takes on sufficient pathogenicity to contaminate surgical wounds and, more rarely, still greater pathogenicity to produce localized and generalized infection, not only following secondary implantation, but also as a primary invader.

Although some authorities still look with skepticism upon the possibility of generalized pyocyaneus infection, there is now sufficient evidence in the literature clearly to indicate its characteristic symptomatology as well as its reality.[6,17,20,35,39,51] To be sure, generalized infection is uncommon and occurs most often in children and debilitated adults,[17] but it may also attack the healthy mature individual.

Pyocyaneus infection is most logically divided into two types, localized and generalized, and these in turn may run acute or chronic courses.

Among the *localized* forms, the common wound infection, discharging a bluish-green pus, needs no discussion. At times the virulence may be increased to the extent that contamination leads to hospital epidemics not only in surgical wounds, but in the umbilical wound and, through contamination of feeding bottles, the enteric tract of the child, resulting in a diarrheal syndrome.[12]

In the eye, corneal involvement is most serious and follows the implantation of a foreign body. Ulcerative keratitis results, often leading to panophthalmitis.[31,45] The clinical course is usually rapid and severe. Evisceration often becomes necessary, but occasionally cases

reach a chronic stage with favorable response to treatment. Dacrocystitis, punctate keratitis and conjunctivitis have also been reported.

Infection of the ear is of two types. In the middle ear it is usually superimposed upon an already existing otitis media. Direct extension to the mastoids and from there to the meninges and brain has been reported. In the external ear the infection appears to be primary. It may be unilateral or bilateral. Onset may be acute or insidious and there is a tendency for the process to become chronic.[23] Subjectively, the patient experiences throbbing and pain and, on examination, diffuse redness and exudation are found. With the development of chronicity, pain recedes and pruritus appears with thickening and scaling of the epithelial surface. The organism may be found in the exudate but pigmentation is not constant. Reports of vaccine therapy[23] are very enthusiastic in this type of infection.

One of the most important of the local types of pyocyaneus infection is involvement of the gastro-intestinal tract. *B. pyocyaneus* is not unusual in the ulcers of agranulocytic angina. Attempts[29,39] to associate the organism with the etiology of this interesting disease have all met with failure, and in the light of our present knowledge of agranulocytosis such findings represent secondary invasion in spite of the work of Lovett[36] demonstrating a depressant effect on the white blood count in guinea-pig inoculations. Likewise, since the organism normally inhabits the gastro-intestinal tract, its recovery from specific ulcers, such as those of tuberculosis and cancer, is not surprising.

Lesions of the pharynx, esophagus, stomach and intestines occur. Diarrhea in children has already been mentioned. Such symptoms occur in adults as well, particularly in tropical regions and in association with generalized infection. Mucus and blood may appear in the stools. Greenish discoloration of the stools has also been noted.

Localized infection often spreads by contiguity and contact. Infection transferred to the exposed surfaces of the body by contact has led to confusion with pellagra.[3,30] The development of mastoiditis and its complications have already been noted. In the upper respiratory passages, bronchitis, lung abscess, bronchopneumonia and pleurisy may follow. Endometritis may follow puerperal infection and in the urinary tract, ascent to the kidneys has resulted from cystitis.

Generalized infection with *B. pyocyaneus* is rare. Fraenkel[19] found only 13 primary cases in 12,000 autopsies. Such infections start from a localized lesion, often in the middle ear or colon. The source may not be known and the infection appear generalized from the onset. A description of the clinical picture is worthy of repetition. Onset is usually sudden in the acute type with symptoms which resemble closely those of other types of septicemia. Gastroenteric symptoms such as nausea, vomiting, and diarrhea, together with cough and dyspnea are the rule. The temperature is high and of the septic type. Generalized pains, in the head, back and extremities develop. The spleen may be palpable. An eruption appears, most commonly maculopapular and red to blue in color. These lesions develop rapidly and fade slowly. Recurrent crops have been noted. Other types of lesion seen are hemorrhagic or ecthymatous, and eruptions resembling erythema multiforme or erythema nodosum. It is clear that confusion with typhoid fever may and has easily occurred in such patients.

The fever known as "13-day fever" or "Shanghai fever" has been traced to *B. pyocyaneus*.[35] The skin eruption, together with splenic enlargement and a febrile course ending by lysis in 2 to 3 weeks, closely resembled typhoid fever, but the occurrence of leukocytosis, the isolation of *B. pyocyaneus* from the blood and excretions together with agglutination reactions as high as 1 to 400 clearly established the diagnosis.

Chronic generalized infection may follow the acute stages, but more often it begins insidiously without the acute pictures described above.[8] Freeman's case is an excellent example,[20] as shown by the long course, irregular septic fever, chills and sweats, a cutaneous eruption, neuralgic pains, especially in the extremities, and paresis and muscle atrophy of the legs. The latter symptoms, paresis and muscular atrophy, are apparently due to the exotoxin which is said in animal experimentation to produce paralysis and wasting. Great emaciation and weakness are also seen in chronic infection, and anemia usually develops.

In such a septicemia, metastatic lesions often develop, involving almost any organ, including those already mentioned in localized infection as well as the liver, gall bladder, spleen, the heart, serous cavities and joints.

Meningitis has already been mentioned as a complication of mastoiditis. Cases[41] have also been reported following infection of the nasopharynx and orbital cellular tissue. Reports are also available describing meningitis following generalized infection, traumata of the brain or spine, and in 1 case, so-called "primary" infection without known portal of entry.[51] Development following spinal puncture[46] is also well known. Symptoms and signs are those of meningococcal meningitis, and need no repetition here. At times symptoms have shown an exacerbation following diagnostic spinal puncture.

Encephalitis ascribed to pyocyaneus toxin in the absence of organisms in the brain[32] has been reported.

Diagnosis of pyocyaneus infection in draining wounds usually follows recognition of characteristic pigmentation of the pus or dressings. Pigmentary change cannot be relied upon, however, because of the lack of its production when the oxygen supply is inadequate. This may happen even with superficial infections, for example in the external ear. Diagnosis must rest, therefore, upon the demonstration of the organism in causative relationship to the lesion,[47] a difficult problem in the gastro-intestinal tract.

In generalized infection the clinical picture is not diagnostic. At times the characteristic skin lesions with gastroenteric symptoms and paresis of leg muscles leading to atrophy may be suggestive, but again the clinical picture may not be typical. Positive blood culture is conclusive, but is not always obtainable especially in the chronic stage. In Freeman's case[20] bile cultures at operation were successful when blood cultures were negative.

Prognosis in localized infection is invariably good, except in involvement of the eye. In generalized infection, prognosis varies from excellent in transient bacteremia[47] to very poor in sudden and severe infections. Recovery is not unusual in chronic generalized infection and in meningitis.

Meningococcemia. The common clinical picture of meningitis with headache, vomiting, fever, eruption, stiff neck, focal neurologic signs and

a positive spinal fluid comes to mind when the meningococcus is mentioned, but the occurrence of meningococcal disease without meningeal involvement is not sufficiently well known. This is all the more surprising when one realizes that 35 years have elapsed since Salomon[43] first reported a case of chronic meningococcemia. Up to January, 1931, Binns and Fothergill[7] were able to find only 19 reported cases in the American literature and over 100 cases in the foreign literature. Such figures can only indicate a lack either of recognition or of recording of such cases, particularly in this country. An increasing number of reported cases since that time supports the supposition that increased recognition of this clinical picture awaits the education of the American physician to the possibility of its presence in febrile disorders. This is particularly important since the clinical picture is sufficiently characteristic to permit a tentative diagnosis before blood culture confirmation is obtained.

Orientation as to the place of both acute and chronic meningococcemia in meningococcus infections may be gained from a brief consideration of the pathogenesis of cerebrospinal fever. There is general agreement that the meningococcus first finds its way into the upper respiratory passages, where it may or may not call forth an inflammatory reaction. From this point on, the theories of infection become divergent. Among them we find the theory of direct extension, which postulates a direct spread to the meninges, for example, by way of the sphenoid or ethmoid lymphatics or by the olfactory nerve. Another group believes that septicemia first develops following upper respiratory infection with hematogenous spread to the meninges. This mechanism is championed by Herrick,[24a,b,c] who, during the World War, demonstrated positive blood cultures preceding infection of the spinal fluid. He divides infection into 3 stages: first, a carrier stage or infectious stage in the upper air passages, usually of short duration leading to a second stage of bacteremia, which, in a short time, usually within 48 hours, is followed by a metastatic phase, in which the meninges are involved in about 90% of the cases. The latter is the stage with which most of us are familiar and may occur sufficiently early to appear as the initial process. While one cannot doubt the possibility of infection of the meninges by direct extension, evidence is adequate to state that in many cases meningeal involvement is secondary to bacteremia.

The observations of Herrick have led Graves, Dulaney and Michelson[21] to classify meningococcemia into two types; first *acute meningococcemia*, of less than a week's duration before localization in the meninges occurs. Into such a group fall those patients with fulminating meningococcemia of sudden onset with marked sepsis, a petechial eruption, a clear cerebrospinal fluid and death within 8 to 24 hours following the initial chill. Such patients are usually in good health and suddenly develop symptoms of overwhelming infection leading to death before signs of meningitis appear. Restlessness, vomiting and abdominal pain quickly develop. Prostration is marked. The temperature varies from high to subnormal values. Stupor is common. Cyanosis or a mottled pallor may develop and a petechial rash makes its appearance, often with great suddenness and especially over the extremities, buttocks and back. In several days these lesions may fade leaving a brown stain. Such a picture is sometimes described as the

Waterhouse-Friderichsen syndrome.[1] Grossly, postmortem evidence of meningitis in such patients is absent or slight.

When bacteremia does not lead to such fulminating infection, the usual text-book picture of meningococcal meningitis generally develops.

The second group in the classification of Graves and his associates is *subacute or chronic meningococcemia*, in which the bacteremia persists more than a week before localization occurs, if it does so at all. Into this group falls the second class of cases now under discussion, meningococcemia with metastatic spread to the joints, heart (endocardium), pleura, conjunctiva and, finally, at times, to the meninges, as well as meningococcemia without evidence of metastatic infection at all.

Chronic meningococcemia displays a clinical picture so characteristic that, if one has the possibility in mind, diagnosis may be made at the bedside. Laboratory confirmation is, of course, necessary. This symptom complex may occur at any age. Ninety per cent of the cases, however, have been found in the third and fourth decades.[42] In an analysis of 68 cases, Dock[15] found only 10 females. However, 41 of the reported patients were soldiers. In civilian practice[2] sex distribution is about equal.

Onset is usually described as sudden[24a] with headache, fever, and chills or chilly sensations. More rarely the onset is insidious, and Stewart-Wallace states it is usually so, with malaise and pain in the limbs. Evidence of upper respiratory-tract infection may be present or absent. A triad of symptoms, intermittent chills and fever, arthralgia, and a skin eruption, makes up the essential features of the disease.

Fever is often remittent and may rise to 104° or more. At times, intervals as long as 10 days may separate the febrile periods.[2] The febrile episodes of all types of malaria may be closely imitated. Dock, in the 68 patients mentioned above, found intermittent fever daily in 49, 2-day cycles repeatedly in 37, 3-day cycles in 21, and 4-day cycles occasionally in 3. Chills or chilly sensations often accompany the recurring bouts of fever.

The eruption may vary in nature, size and distribution. It usually makes its appearance in the first week. Rarely, it may be absent. The extremities are the most frequent site, but it also occurs on the chest and face and, less commonly, on the abdomen and back. The lesions are usually maculopapular and rose red in color but may vary from faint pink to deep red. Size varies from that of a pinhead to several centimeters in diameter. Disappearance time varies from 36 hours[7] to 7 days[48] and the remaining stain which has been described as brown to bluish-red gradually fades. New lesions often appear with recurring fever. Erythema multiforme and erythema nodosum may be simulated. Tenderness is sometimes present. Petechiæ are common and do not disappear on pressure. Pustules have been described.[2] Biopsy of lesions from one of Stewart-Wallace's cases disclosed no specific microscopic pathologic changes.

Arthralgia may be a striking feature of the disease. Such pains are usually migratory without evidence of inflammation in the joints. Swelling and tenderness may occur, however, but suppuration of the joints is uncommon.

Physically, these patients may show a paradox of severe sepsis and an apparently good general condition[40] especially between bouts of

fever. The eruption and fever may be the only positive physical signs, although at times the spleen may be palpated.

Differential diagnosis may be difficult. This is especially true with subacute bacterial endocarditis, particularly since endocardial metastases resulting in bacterial endocarditis may be a part of the disease itself. The occurrence in both diseases of embolic phenomena in the skin, kidneys and spleen, the septic course, joint pains without local inflammation, and positive blood cultures[40] demonstrate their similarity. Typhoid fever, brucellosis, malaria, rheumatic fever, miliary tuberculosis, gonococcal sepsis, erythema multiforme and erythema nodosum are also confusing.

Although our particular interest lies in those patients having had no meningitis until, perhaps, the terminal stages of the disease, such a picture may develop following meningitis.[33] The clinical picture is not peculiar to any one type of meningococcus.[48]

The course of the disease varies from several weeks to many months and prognosis is, in general, good. Complete recovery has taken place in 75 to 90% of reported cases.[7,48] In fatal cases, endocarditis or terminal meningitis are common, particularly the former, but recovery has often been reported with both of these complications and their exact status in prognosis is not yet clear. Other complications worthy of mention[15] are anemia, empyema, suppurative orchitis, interstitial nephritis, thyroiditis, prostatitis, retinal hemorrhage, iridocyclitis, and extradural abscess.

Final diagnosis rests upon positive blood culture. At times there may be difficulty in the isolation of the organism and negative cultures do not rule out the disease. Enriched media are essential for good results. McLean and Caffey[38] have pointed out the value of smears from the purpuric spots as an aid in the early diagnosis of meningococcic bacteremia. Smears are made from the material obtained by stab wound from the purpuric area and stained for Gram-negative intracellular diplococci. In 18 cases examined by them 15 (83%) were positive. Such a procedure is not a substitute for a blood culture but may lead to a tentative identification of the organism 12 to 72 hours before cultures are available for analysis. Agglutination reactions are, in general unsatisfactory. There appears from recent reports[2] to be no contraindication to the use of diagnostic spinal tap in the absence of meningitic signs.

Treatment is not to be considered here. Adequate discussions may be found in the more recent literature.[2,7]

Enterotoxic Staphylococcal Food Poisoning. Food infection of the type characterized by gastro-intestinal symptoms, nausea, vomiting, abdominal cramps, and diarrhea with varying degrees of prostration, which occurs in epidemics, persists for 24 to 48 hours and entails an extremely low mortality has invariably been associated with the salmonella group of organisms. More recently, however, the increasing number of such outbreaks ascribed to staphylococci has created considerable interest in the potentialities of this organism in the production of such symptoms. The bacteriologic aspects of the staphylococci have recently been reviewed in these columns[25] but little was said at that time concerning clinical and epidemiologic problems of food poisoning.

In this disease, like many others of recent general recognition, first

description goes back many years. Barber[4] in 1914 noted the occurrence of the usual symptoms of food poisoning in himself and other individuals visiting a certain farm in the Philippines. He traced the cause to milk infected with staphylococci and noted further that fresh milk was harmless, and that its effectiveness in the production of symptoms developed only after standing some hours at room temperature. He also described the short incubation period of approximately 3 hours which has characterized subsequent outbreaks reported by others.

Despite Barber's early report, interest in, and recognition of, the staphylococcus as a cause of food poisoning has become general only in the past 6 years. Further reports of milk infection[13,44,49] have appeared, but the chief offending foods have been baked goods, particularly those with cream fillings.[26,37] Cheese and gravies have also been responsible.[28] In all, the symptomatology has been uniform. The incubation periods have been short. Approximately 3 hours after the ingestion of contaminated food, nausea, vomiting, and diarrhea make their appearance. In salmonella infection, the incubation period is often longer with a meal intervening between the intake of infected food and the development of symptoms.

The shortness of the incubation period suggests the ingestion of a toxin rather than the development of infection within the patient. The report of Barber also suggests a toxin in that fresh milk was harmless unless it stood several hours before ingestion. Numerous investigations on volunteers have confirmed these suspicions, in that the ingestion of sterile filtrates of the isolated organisms has in many instances duplicated the symptoms in their entirety.

The modes of contamination of milk are many. In Barber's original description[4] and in several outbreaks in the United States[13,44] mastitis of a recurrent type, garget, was demonstrable. Crabtree and Litterer[13] found, in two cows supplying milk to the group under observation, udders with pus pockets periodically releasing large numbers of staphylococci. In Tanner and Ramsey's report,[49] intentionally contaminated milk was ingested for experimental purposes. Ice cream made from contaminated milk has also caused symptoms.[44]

The sources of contamination in outbreaks due to baked goods are not as evident. Presumably contaminated ingredients or the introduction of infection during the preparation of foods might occur. Jordan and Burrows[26] were unable to find staphylococci in significant numbers in the ingredients used in the production of known contaminated baked goods. Milk was not examined. Batter prepared by 7 different men in one of the implicated bakeries disclosed similar results. However, during the process of preparation, especially of cream-filled pastries, abundant opportunity for contamination with staphylococci exists. Since Jordan, Dack and Woolpert[27] have shown that the product of the bacteria responsible for symptoms may resist boiling for 30 minutes, one must bear in mind, as the source, ingredients containing the enterotoxin before exposure to heat. Baked goods are likely to be kept at temperatures quite favorable to the multiplication of any bacteria present.

The recognition of a particular type of staphylococcus responsible for such symptoms would be an exceedingly valuable contribution to both diagnosis and prevention. Jordan and Burrows[26] have carried

out studies to settle these problems. They have definitely established the fact that there are no characteristic bio-chemical or serologic reactions. Staphylococci of diverse origin and different cultural and agglutinative characteristics may elaborate a substance which is toxic on ingestion. They also found that strains from normal throats, from human septicemia, osteomyelitis and local abscess may produce a substance which induces vomiting in human volunteers. These organisms were either *S. aureus* or *albus* and differed in speed and type of gelatin liquefaction and in the degree of hemolysin production. Partial confirmation of these results has been reported by Chinn.[10]

The ubiquity of the staphylococcus and the infrequency of outbreaks of food poisoning caused by it suggest that either this cause of food poisoning is often unrecognized or unusual strains of the organism and exceptional environmental circumstances are necessary for the production of the enterotoxin.[16] Dolman, in a series of procedures designed to support the latter views, demonstrated the independence of the exotoxin and the food poisoning substance. His results indicate that the enterotoxic substance, the nature of which is still obscure, is probably produced by only a few strains of staphylococci, as a special metabolite, the formation and excretion of which are favored by a semifluid medium and an atmosphere high in carbon dioxide. Although he states that it is difficult to imagine such circumstances in contaminated foodstuffs, baked goods, particularly of the cream-filled variety, appear to this Reviewer to be an ideal site. They are semisolid, but the carbon dioxide content, under these circumstances, is an open question. Definite establishment of Dolman's views would explain the infrequency of staphylococcal food poisoning in the face of the universal distribution of this organism.

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PEDIATRICS

UNDER THE CHARGE OF
ALVIN E. SIEGEL, M.D.
MACON, GEORGIA.

BIRTH TRAUMA WITH SPECIAL REFERENCE TO INTRACRANIAL HEMORRHAGE.

The injuries that are incurred by the child at birth are not limited to the head nor to the intracranial contents although the latter comprise a very large group. According to Holland[7] a complete list of the injuries that are seen would include every tissue and organ of the body. However, intracranial injuries are the commonest type of injury and present the most important problems as regards etiology, prevention, diagnosis and treatment. Damage to other than intracranial structures may be enumerated as follows: 1, skin and subcutaneous tissues anywhere but chiefly in the scalp; 2, muscles—most often the sterno-cleido-mastoid; 3, fractures of the bones in the skull, clavicle, humerus and femur in the order of their frequency; 4, separation of epiphyses; 5, rupture of or hemorrhage into abdominal viscera such as the liver or the suprarenal; 6, damage to thoracic viscera which is rare; 7, peripheral nerve injury such as the facial nerve or the brachial plexus; 8, direct injury to or hemorrhage of the eye; 9, injuries to the spinal cord or to the vertebral column. Damage to the spinal cord is a commoner cause of fetal and neonatal death than is generally supposed. It may occur during the forcible extraction of the aftercoming head or large shoulders in head presentations. The statistical figures of this lesion are inaccurate because even where autopsy has been made examination of the cord is neglected.

Intracranial injuries present the most frequent form of birth trauma. In addition, they give rise to the most serious and to the most dangerous symptoms. They result either with normal or with excessive pressure on the head. Normal pressure leaves no observable effect on the head except perhaps a moderate amount of moulding. Excessive pressure may result in excessive change in the shape of the head, overstretching and tearing of the dura mater septa and rupture of certain vessels, or there may be a rise in intracranial pressure sufficient to obstruct the

venous sinuses and cerebral veins and produce cerebral congestion and edema. Adair,[1] in a series of 961 autopsies on new-born infants, found that the largest single cause of death was trauma at birth, and this comprised 31.2% of the cases. Grulee[5] pointed out that, in examining statistics concerning the new-born, it is extremely difficult to find any which will bear the light of criticism. For the most part this is due to the fact that the figures are based upon the causes of still-births and neonatal deaths. Yet there are many cases of intracranial trauma that do not die. Statistical records of these are rare and often unreliable. While we have some knowledge of the frequency of intracranial hemorrhage as a cause of death, little information is available as regards the actual frequency of occurrence of this complication. Therefore, reports of large groups of deliveries with accurate clinical, laboratory and pathologic records are extremely valuable. The report of Tyson and Crawford[15] may be considered as such. They studied the records of the deliveries at the Philadelphia Lying-in Hospital from October 1, 1927, to December 1, 1929. During this time there were 2256 deliveries. Of this group 78 babies were still-born, a percentage of 3.46. The living births were 2178 with 81 deaths or a mortality rate of 3.71%. Of the 78 still-born infants autopsy was secured on 53, with permission to open the head in 31. In this group there were 11 cases of intracranial hemorrhage or an incidence of 35.4%. Of the 81 deaths occurring after delivery 66 came to autopsy with examination of the brain in 56. Intracranial hemorrhage was found in 18 (32.1%). After careful study of all cases, 16 additional babies were diagnosed as cases of intracranial hemorrhage. These were discharged as cured or greatly improved by treatment. In the total group of 2256 deliveries there were 45 definite cases of intracranial hemorrhage or an incidence of 1.9%. These figures do not include mild cases that were symptomless or had mild symptoms that escaped notice so that the actual incidence of this complication may be somewhat higher.

While many cases are the result of active causative factors which are usually recognizable, some are encountered without any demonstrable cause and are probably due to certain predisposing factors, one or more of which are often present. Bland[2] pointed out a number of these predisposing influences. The parity of the mother is a very definite factor, as the accident is much more frequent in the first delivery than in subsequent labors. It is said that this is especially true with the birth of male infants, but why this frequency exists is not known. Intracranial damage is prone to occur in prolonged and difficult labor, as is met in contracted pelves with delivery occurring either spontaneously or otherwise. Judicious instrumental delivery may be less likely to be followed by intracranial damage than unwisely governed spontaneous labor. There is a marked increase of predisposition in technically difficult and imprudent forceps delivery. In complicated breech delivery, especially in cases associated with hasty, unskilled extraction of the after-coming head, damage is likely to occur. This method of delivery is held accountable for a large number of cases of brain injury. The occurrence of intracranial trauma is far more frequent in premature and immature infants. There are several causes for this. One cause is the fragility of the blood-vessels in these children. Another is in complete anatomical development of the strengthening fibers of the tentorium. Immaturity and prematurity are among the chief predis-

posing factors. Difficult delivery of the aftercoming head following version is another frequent obstetrical cause of intracranial injury. The indiscriminate use and excessive dosage of pituitrin to stimulate uterine contractions in the second stage of labor often causes damage to the brain or its membranes. Biochemical changes in the blood and constitutional diseases such as syphilis are often included as predisposing factors, but some observers do not agree on this point although it may be reasonable to assume that a hemorrhagic tendency bordering on the pathologic may be a predisposing factor in some cases.

The most frequent result of intracranial trauma is hemorrhage. The location of this varies. According to Litchfield and Givan[10] supratentorial hemorrhage is the most frequent. This may be over the vertex or under the hemispheres. Subtentorial hemorrhages are next in order of frequency followed by intraventricular hemorrhage, hemorrhage into the brain substance and hemorrhage into the spinal canal. A very lucid presentation of the lesions produced by and mechanism of intracranial injury was given by Holland (*loc. cit.*). He stated that overstretching and tearing of the dural septa followed alterations in the tension of the septa accompanying alterations in the shape of the head. Because of the nature of the attachment of the septa to the cranial bones this is inevitable, and the fact can be demonstrated on a fetal head by reflecting the scalp and removing sufficient of one parietal bone to allow the cerebral hemisphere to be removed and the septa to be viewed from that side. On compressing the head in the suboccipitobregmatic diameter, the head becomes shortened anteroposteriorly by forward displacement of the occipital bone and heightened vertically by bending and elevation of the vault. If at the same time the septa are observed, it will be seen that the middle two-thirds of the falx cerebri and the tentorium will become stretched and tense. In addition, the septa move as a whole as will be appreciated by watching the anterior point of junction between the falx and the tentorium, which is the site of entrance of the vein of Galen into the straight sinus. This becomes displaced upwards and forwards, the latter movement being the much more pronounced. If the pressure is increased by stronger compression, the tentorium tears near its free border just below its junction with the falx. The bending of the bones and the excursion of the vault is resisted by the septa and when the septa tear, a restraining influence is removed. The septa exert a protective influence during labor against excessive alteration in the shape of the head. Reasonable moulding of the head is beneficial, but undue distortion may jeopardize life of the fetus by producing intracranial disturbances, the most important of which is hemorrhage from the overstretching and rupture of certain vessels. The view that the septa are designed to take stress is emphasized by the fact they contain strengthening bands and fibers arranged along the lines where stress is most likely to occur. These bands are developed in order to withstand the effects of excessive stress during labor. There are an anteroposterior and a vertical system. The latter consists of two opposing sets of convergent fibers which meet in their points of convergence. From above downwards fibers converge from the middle two-thirds of the falx, and from below upward fibers from the tentorium converge. They meet in a strong band which has been called the anterior vertical band of the tentorium. This band is subjected to stress in almost every labor, and is the usual site of tentorial tears. This theory

of cranial stress is supported by the tears of the tentorium and falx as found in dead fetuses. Tentorial tears are nearly always situated in what has been described as the area of greatest stress, just below the junction with the falx anteriorly and implicating the anterior vertical band. Tears of the falx cerebri are found relatively infrequently and they usually occupy the middle two-thirds and are elliptical with the long axis lying in the line of greatest stress. The tears may affect one or both sides of the tentorium and may be complete or incomplete. The latter involve only the superficial layers. Complete tears usually involve the free border of the tentorium but sometimes there is a perforation. Tears of the dural septa may bleed very little or not at all and are not always fatal injuries of themselves. They indicate excessive intracranial stress and the mortal lesion may be the accompanying intracranial effects such as cerebral hemorrhage and the asphyxial effects of intracranial pressure.

From the etiologic standpoint there are two varieties of intracranial hemorrhage, traumatic and asphyxial. Gross hemorrhage is probably always traumatic. It occupies the subdural space and is nearly always associated with tears of the dural septa. Asphyxial venous engorgement is a most important contributory factor in traumatic hemorrhage, for engorged veins rupture more easily and bleed more freely. Clear postmortem evidence of fetal asphyxia is usually found in cases of gross hemorrhage. A clear differentiation between traumatic and asphyxial bleedings is not always possible, and they often occur together. Engorgement of the cerebral veins may be part of a general asphyxia, or may be a local condition due to obstruction of the cerebral veins from cerebral compression or traumatic cerebral asphyxia. When large vessels have ruptured it is possible to trace definitely the source of the hemorrhage. Large veins commonly found ruptured are the vein of Galen and the cerebral veins entering the superior longitudinal sinus. Sometimes the venous sinuses themselves are ruptured, the most common one being the straight sinus and more rarely the superior longitudinal and lateral sinuses. The site as well as the size of a hemorrhage is of importance as regards the effect produced. Large hemorrhages kill by compression of the cerebrum with damage to the respiratory centers. Hemorrhage in the posterior fossa or infratentorial hemorrhage is more damaging than elsewhere in the subdural space. In studying the brain itself there are found petechial hemorrhages and small areas of necrosis in a very high proportion of newborn children. The hemorrhages are definitely related to the distribution of the tributaries of the vein of Galen, the vena terminalis, vena lateralis ventriculi and vena chlorioidea. Necrotic areas appear as opaque yellowish spots, often in confluent groups, in the central white matter and basal ganglia around the third and lateral ventricles. Microscopic or macroscopic hemorrhages can be found in 95% of infants during the first weeks of life.

Prolonged cranial compression may obstruct the venous sinuses and cerebral veins and produce asphyxia of the brain and medulla. The lesions found at autopsy are intense congestion and edema of the brain and meninges. This still further increases the intracranial pressure. This condition is sometimes classed under the heading of intracranial lesions without hemorrhage but perhaps a better term would be traumatic cerebral asphyxia. The effect of asphyxia on the respiratory

center would be to stimulate it, and the fetus would make intrauterine respiratory efforts. This is evidenced in some cases at autopsy by the finding of amniotic fluid in the trachea or bronchi. The alteration in the intrathoracic pressure as the result of the inspiratory efforts would lead to venous engorgement of the whole venous system or a generalized asphyxia. While such an asphyxia would not necessarily be fatal, if it were prolonged it would lead to increasing paralysis of the respiratory center causing the center to fail to respond to stimuli after delivery.

Although the bones of the cranium are freely movable and although this allows for considerable overlapping or moulding, injury of certain of these bones occur. Hemsath[6] reported 32 cases of separation of the posterior intraoccipital synchrondosis. He called attention to the fragility of the base of the skull even in the full-term fetus. The synchrondosis between the squamous and lateral portions of the occipital bone, because of its weakness and its close proximity to the medulla oblongata, makes the base of the skull susceptible to grave trauma during delivery. This injury consists of a separation, which may be called an osteodiastasis since it is not really a fracture. Hemsath found 32 cases in 166 consecutive autopsies in still-born and neonatal deaths. Osteodiastasis was found in 48% of the autopsies on patients delivered by version with breech extraction; in 33% each of forceps deliveries and of primary breech extractions, and in 2.3% of spontaneous deliveries.

The early symptoms of intracranial hemorrhage in the new-born do not present a definite fixed picture. The symptoms vary according to the location, type and extent of the hemorrhage. As regards the extent of the hemorrhage, this varies from very extensive loss of blood to very small bleeding and there are undoubtedly many hemorrhages of such mild type that they are not recognized. Moore[12] gave as the most common early symptom signs of cortical irritability, such as crying, and heightened irritability of the motor centers such as twitching of the muscles, spasticity and convulsions. In some cases of ventricular or subtentorial hemorrhage the infant may be very quiet or even comatose, but usually even in these cases there are some early signs of cortical irritability. These will always tend to dominate the picture, even if the cortex itself is not directly affected by the hemorrhage but where edema or pressure of a hematoma from beneath is producing the irritation. The symptoms vary from mere increase in spasticity of the extremities with occasional twitchings of the muscles to generalized convulsions. Perfectly normal babies may present the former picture at times so that these symptoms alone are not diagnostic. In the average hemispheric case there is twitching or convulsive movement of the lower extremities either unilateral or bilateral. In cases where the hemorrhage is infratentorial the cranial nerves may be involved first with convulsive movements of the facial muscles or of the eye muscles. In cases where the hemorrhage is extensive so that the intracranial pressure is raised markedly there may be a series of general convulsions. These begin with clonic convulsions of the extremities, strabismus, nystagmus, opisthotonos, respiratory disturbance, and loss of consciousness. In some of the ventricular hemorrhages the infant may have tonic convulsions similar to those seen in tetanus. Another important symptom of intracranial hemorrhage is refusal to nurse. This is probably due to a disturbance of the normal nursing reflex, which in the normal infant

is brought out by putting the nipple against the lips. This sometimes occurs also in premature or immature babies so that it cannot be considered as pathognomic although it is always highly suggestive. Disturbance of respiration is a very frequent symptom. This may take the form of very slow breathing or a very rapid breathing or an irregular breathing. Slow breathing is a sign of subtentorial or intraventricular hemorrhage which causes direct irritation or paralysis of the medullary centers. Cyanosis is another frequent symptom. It may be an accompaniment of the respiratory embarrassment due to the direct effect of the hemorrhage or to the cessation of breathing due to a convulsion. In some cases atelectasis is associated with the cerebral injury as a result of the shallow breathing. Signs of increased intracranial pressure such as bulging of the fontanelle and increased pressure of the spinal fluid are often encountered. Minute hemorrhages or subtentorial hemorrhages do not cause bulging of the fontanelle. The increased spinal pressure can be shown only by spinal puncture. Bloody spinal fluid is an absolute diagnostic point provided it can be certain that the blood is not the result of puncture of a vessel in making the tap. The presence of degenerated red blood cells, cellular debris and hematin pigment suggest blood from intracranial hemorrhage while normal appearing cells suggest blood resulting from the spinal puncture. Paralysis is a late sign of intracranial hemorrhage except in the most severe cases. In these cases it is often a terminal symptom. Ocular changes occur but their demonstration is difficult. These consist of mild edematous blurring of the upper and lower margins during the first few days of life with later an edematous blurring of the entire surface of the nerve head and all of its margins. Change in the coagulation time of the blood is another symptom of intracranial hemorrhage. A prolonged coagulation time is a direct indication for the injection of whole blood.

Shannon[14] recognized the confusion frequency of cerebral complications in the new-born with indefinite recognition of the underlying conditions, but with most of the burden placed upon obstetrical error. He called attention to the frequent existence of disturbances which are often responsible for the symptoms of intracranial involvement or may be present together with an actual cerebral trauma.

Other conditions besides trauma give rise to a clinical picture that closely resembles that of birth injury. In fact some of these may be coëxistent with the picture of cranial injury. Shannon stated that a constitutional syndrome exists frequently during the neonatal period. This may be independent of obstetric abnormality and is often responsible for the symptoms of cerebral disturbance. This condition is tetany and it may be only a part of a syndrome consisting also of a tendency to generalized edema and of edema of the brain. It may be that the latter is responsible for many of the symptoms usually attributed to cerebral hemorrhage and other injury of the brain. According to Shannon, tetany results from some interference with the calcium metabolism which results in a low ionic calcium content of the blood and tissues. Such causes are excess of sodium and potassium, calcium starvation, parathyroid deficiency and alkalosis. In addition to the symptoms produced by the lowered calcium concentration of the blood of the infant, it is quite possible that the low blood calcium content may favor loss of coagulability of the blood and predispose more readily

to hemorrhage as well as to edema. The cerebral symptoms of tetany are the most important. They are the signs of cerebral pressure. The pulse may be slow, though the slowness may not be constant. It may be noticeable only when the infant is perfectly quiet, the normal rapidity returning almost immediately when the infant is made to cry or is otherwise disturbed. In the extreme phase this process may progress into the cyanotic attack. The latter may come on either by holding the breath while crying or while the infant is perfectly quiescent. In both cases the heart is slowed almost to a complete cessation of its beat and respiration is suspended for a varying length of time, and the infant is to all appearances dead. When recovery occurs, its onset may be heralded by a deep gasping inspiration following which both respiration and pulse assume their normal characters. In some cases the heart beat may become first more rapid and stronger, followed shortly by the faintest respiratory effort, which together with the cardiac action gradually assumes the normal. Usually the cyanosis, which is most extreme during the attack, entirely disappears in the intervals, though this may not always be true. At times when marked tetany is present, it seems that respiratory irregularity may occur as the result of spasm of the diaphragm, similarly to what is noted in other types of tetany. Typical generalized convulsions may occur. Strabismus, pupillary irregularity and spasmodic downward turning of the eyes may be noted also. In cases showing these symptoms the diagnosis of increased intracranial pressure may be supported by a definitely bulging fontanelle. More often the fontanelle is extremely tense, the sutures being separated and the whole cranium giving the impression of an inflated ball. Improvement of the condition follows administration of calcium, and the condition may clear entirely if it is the result of tetany alone. In those cases with cerebral injury present with the tetany, improvement may be only partial.

The diagnosis of intracranial hemorrhage may not be easy. According to Loeber,[11] in order to arrive at a diagnosis of intracranial hemorrhage, account must be taken of the history of the delivery, the signs and symptoms of the new-born suggestive of the condition, the recovery of bloody cerebrospinal fluid after puncture and an improvement or relief of the symptoms following the puncture. It is more likely to be found after prolonged labor, precipitate labor, in large or oversized infants and breech extractions alone or following version. Infants born under these conditions and who show signs after delivery of a difficult or abnormal respiration, or those having asphyxia, and those with tense, bulging fontanelles suggest the diagnosis of intracranial hemorrhage. Other suggestive symptoms are a whining, high pitched cry and refusal to nurse or difficulty in nursing. The heart is usually rapid with strong sounds and a full pulse, but cyanosis may be constant or intermittent. There is no real pathognomic sign unless it be bloody cerebrospinal fluid. Even this may be misleading unless it is certain that the blood in the fluid is not the result of puncturing a vessel in making the puncture. Levinson[9] and others recommend spinal puncture for the purpose of establishing the diagnosis, but he also considered it of therapeutic value. Loeber (*loc. cit.*) recommended the cisterna route as the method of choice in obtaining fluid for diagnosis as well as a therapeutic measure because of the ease of access and because the posture of the baby during the procedure does not tend to exaggerate

the already existing trauma and symptoms. In the prevention of birth injury the responsibility is entirely with the obstetrician at least insofar as avoidance of such procedures as are likely to threaten injury to the child is concerned. From all sources it is evident that attempts to hasten the onset of labor, to shorten the duration of labor and to allay pain are large factors in the resulting ill effects to the baby. Galloway[4] emphasized that nothing should be done to hasten delivery until the head is visible or on the pelvic floor. The use of solution of posterior pituitary and other preparations to cause more rapid descent of the head is firmly contraindicated. Episiotomy is indicated in order to relieve pressure as the head comes through the narrow vaginal opening, especially in cases where the baby is premature. Premature rupture of the membranes either for the induction of or to hasten labor is contraindicated because of the negative pressure exerted on the presenting parts. Application of forceps is contraindicated as it may still further increase the pressure, but outlet forceps in conjunction with episiotomy usually result in fewer hemorrhages. In the use of forceps it is most necessary to have a set-screw or some means to prevent excessive pressure. In cases where there has been excessive moulding of the head of the infant this moulding should be released slowly. All attempts at resuscitation by violent motions with the baby must be avoided. Too prolonged labor also is dangerous. Cesarean section after a moderate test of labor is fairly safe or early in those cases where it is known that delivery through the usual way will be impossible. According to Galloway, breech delivery and version with breech extraction give higher incidence of birth trauma than any other type of delivery. The fetal mortality is also correspondingly high. There are several pertinent facts relative to breech extraction which demand attention. The unnecessary haste displayed by the average operator is most objectionable and after this the most undesirable factor is the lack of complete relaxation and dilatation of the soft parts. Breech extraction requires complete dilatation and deep ether anesthesia. Episiotomy is indicated in practically every case. Certain fundamental precautions in addition are necessary. The operator should avoid pressure on the fundus, extreme angulation, excessive suprapubic pressure and dangerous traction. The latter is likely to cause damage to the cord.

In the treatment of intracranial birth injuries Kugelmass[8] stressed primarily the need for gentle manipulation in the asphyxia of the newborn not only because strenuous methods are productive of bodily trauma but also because they either aggravate an already existing intracranial injury or may produce dural injury especially in the premature infant. In the asphyxiated baby the veins are engorged and as a result are more easily damaged as many babies have a tendency towards bleeding. Mouth-to-mouth insufflation is the method of preference for a number of reasons. The procedure is not forcible, the baby's body is essentially at rest and the presence of from 3 to 4% of carbon dioxide in the operator's breath favors the stimulation of respiratory activity. In addition, the Flagg apparatus for the administration of carbon dioxide-oxygen mixture is recommended together with the employment of the Drinker respirator and in some cases the oxygen tent has proved useful. Atropine and alpha lobelin have been recommended as well as other respiratory and cardiac stimulants. Pressure symptoms resulting from intracranial hemorrhage or the marked cerebral edema

often seen as an attendant phenomenon may be alleviated either through the vascular route or through the cerebrospinal canal. By the vascular route relief of pressure is obtained by the intravenous injection of hypertonic glucose solution. By the spinal method pressure is relieved by spinal, cisternal or ventricular puncture. The natural tendency of newborn infant towards hemorrhage or a definite bleeding should be treated by the injection of whole blood into the gluteal areas. Birth shock should be treated by the application of heat; by the administration of fluid with some nourishment if possible. Kugelmass recommends the administration of a solution combination containing 3% of gelatine, 5% of glucose and 0.5% of sodium chloride by the Breck feeder every hour. After the second day evaporated or condensed milk mixtures should be used if maternal milk is not available. The early and prompt improvement of nutrition is essential. Surgical intervention by trephining has resulted in a high mortality rate.

Riesenfeld[13] recommended posture as a procedure in controlling the intracranial hemorrhage of the new-born, as well as method for the prevention of the condition. In his service all babies are placed in an almost vertical position with the head slightly extended and maintained in this position by small pillows. This position is maintained for from 8 to 10 days. In cases of cerebral hemorrhage it is continued for a longer period. It is claimed by this author that in the upright position the sagittal venous pressure is materially lessened, a fact which has been shown by animal experimentation.

A proportion of the infants that survive intracranial trauma at birth develop and grow with no apparent evidence of the trouble that they experienced during the early days of life. Others in varying degrees are crippled mentally and physically. Carlson and Klingman[3] based their report on studies made on persons injured at birth, who were treated at the Neurological Institute of New York. They found that while the pathologic changes underlying the conditions were inadequately defined, the manifold symptoms indicated widespread lesions scattered through most of the nervous system including the spinal cord. It seemed probable that the sensory area and the motor cortex were involved to a greater extent in the choreoathetotic and spastic patient than is usually supposed. The evident influence of such factors as fear, concentration, attention and soft-consciousness in increasing the abnormal movements or posture of certain children definitely indicated the probability of damage to the higher centers and emphasized the necessity for control of these subjective feelings as necessary to effective training of the muscles. They extended their investigations into the field of conditioned reflexes and especially into that of psychic activity. Their results were encouraging and justified the attempts to train or recondition acceptable patients with spasticity and choreoathetosis. In planning treatment, it is necessary not only to estimate the mental level of the patient, but also to eliminate as far as possible such special disabilities as those of speech, hearing and vision. The majority of disturbances of speech concern expressional speech and are a part of the general motor disability. Disturbance of speech was found so closely linked with the general spastic condition that improvement was not possible often until the patient had learned to control the larger groups of muscles. When this coördination was obtained speech improved not infrequently without special training.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 17, 1937.

The Intercellular Substance of the Brain Cortex (Nissl's Cerebral Gray). Its Physiological Significance. A. E. TAFT (Laboratory of Psychiatry, Philadelphia General Hospital). Fifty years ago the presence of an intercellular substance in the brain cortex was much studied and generally acknowledged. More recently, it has been almost entirely ignored both anatomically and physiologically. Intercellular substance in other tissues has received considerable recent attention. Its presence in the developing embryo has been observed and described. It has been demonstrated by a number of investigators that this substance has a close relationship with vitamin C, as shown in scurvy, a condition in which there is lack of its formation. This lack is clinically evident in the test for capillary resistance. In paresis, the alteration of the intercellular substance of the brain cortex has been identified by means of fresh tissue in the dark field by this author, and by others in fixed and stained material. The characteristic microscopic appearance of the brain cortex in paresis has been described as a disturbance of cell lamination, giving a "wind-blown" effect. The relation of vitamin C to malaria treatment of paresis has been studied particularly by Plaut and von Bülow, who found that there is a primary fall with a later rise above the degree which existed before treatment. They also found that vitamin C is present normally in greater amount in the cortex than elsewhere in the brain. The writer has drawn an analogy between this cerebral gray and the proteins of blood serum, which are also intercellular substance. Microphotographs show their similarity of appearance. The physiologic importance is emphasized. Since it has been demonstrated that there are no lymphatics in the brain, it seems probable that this strongly hydrated, finely particulate material acts both as a distributor of brain tissue fluids and as a necessary protection to the brain cells. Microphotographs illustrate normal cortical intercellular substance; a comparison of the cortex in the newborn and more mature rat; comparison of normal and senile cortex and normal intercellular substance compared with that in paresis.

The Relation of Dietary Protein to the Formation and Storage of Gonadotropic Hormone in the Pituitary Gland of the Rabbit. MAURICE H. FRIEDMAN and GERTRUDE S. FRIEDMAN (Laboratory of Physiology, University of Pennsylvania). The pituitary gland of the estrus rabbit contains enough gonadotropic material to cause ovulation in 10 or more rabbits. Copulation causes a rapid and almost complete discharge of the gonadotropic material so that 24 hours postcoitum the gland contains less than enough material to cause ovulation in one rabbit. For several days following coitus, during the rapid growth of the corpora lutea, the pituitary is apparently unable to store significant amounts of the gonadotropic material. At the 6th day postcoitum, however, there is a sharp rise in the gonadotropic content of the gland, to a level about two-thirds of the estrus level, and by the 10th day the estrus level is again attained. These findings confirm the original work of R. T. Hill, and this curve of restitution of the gonadotropic content after coitus was used to determine the effect of various dietary regimes on the rate of formation and storage of the sex-stimulating hormone of the pituitary. It was found impossible to influence this curve significantly by protein restriction, even though the experimental animals were kept on a protein-free diet for 17 days before and 8 days after coitus—a total of 25 days without dietary protein. Despite this protein deficiency, and in the face of loss of body weight, the experimental animals were able to form and store the gonadotropic principle at a rate similar to that of control animals which were on a 16% protein diet, and which were gaining weight at the rate of 200 grams a week.

The Adrenals of Rats After Thyroidectomy and Gonadectomy, Considered in Relation to Pituitary Histology. ISOLDE T. ZECKWER (Department of Pathology, University of Pennsylvania). It is known that when one adrenal is removed, the other undergoes compensatory hypertrophy only when the pituitary is present. It is reasonable, therefore, to search for a type of cell in the pituitary that is responsible for adrenal growth.

In the present experiments, the marked quantitative and qualitative alterations in cellular make-up of the pituitary consequent upon thyroidectomy and gonadectomy did not prevent the normal compensatory hypertrophy of the second adrenal after the first was removed. "Castration cells" and "thyroidectomy cells" can be excluded as cells controlling adrenal growth, as their numbers bear no relation to adrenal weights. Since acidophils are absent or greatly reduced after thyroidectomy, yet compensatory adrenal hypertrophy occurs, acidophils can be excluded as responsible for adrenal growth. In pituitaries of rats both thyroidectomized and gonadectomized there remain, in addition to the two types of cells reacting to these operations, only non-secretory chromophobes and unaltered basophils. By this process of exclusion the suggestion is made that adrenal growth may depend upon a type of basophil that is different from the cells that react to gonadectomy and thyroidectomy. The hypothesis is proposed that there may be distinct types of anterior pituitary cells which cannot be differentiated from each other under normal conditions, but which can be dissociated when the pituitary is altered by ablation of thyroid and gonads.

The Effect of Choline and Sucrose Feeding Upon Liver Glycogen and Lipids. H. M. VARS, S. GOLDSCHMIDT and I. S. RAVDIN (Harrison Department of Surgical Research, University of Pennsylvania). Best and his coworkers[2] have presented evidence from which they conclude that choline, naturally occurring in the food, is an important factor in determining the level of liver fat produced by diet. Diets which contained little or no naturally occurring choline resulted in a massive deposition of fat in the liver. Choline chloride fed to such animals led to a decrease in liver fat. No satisfactory explanation of the mechanism of this process has been advanced.

Our findings are in agreement with those of Best *et al.*, that choline chloride added to the dietary of rats, whose livers contained about 40% of total lipids, resulted in a diminution in the fat content. In addition we have shown that accompanying the fall in liver fat the liver glycogen increased. In an animal on an adequate diet increase in the liver glycogen usually results in a fall in liver lipid. Hence the results may be explained either as due to the action of choline in mobilizing liver fat back to the fat depots or in metabolizing it, as Best has postulated, or that possibly the primary effect of choline is to cause a deposition of liver glycogen with the secondary depletion of liver fat as a consequence. Any explanation of the action of choline must take this latter possibility into consideration.

In agreement with Channon[3] and later Best,[1] we have found that on a choline-poor diet, in which alcohol-extracted casein is the source of protein, fat is deposited in large amounts in the liver only when the protein calories are below 10% of the total calories of the diet.

A choline-free diet, in the form of sucrose as the sole source of food to the rat, has given divergent results in our hands. In the larger number of animals the liver fat has decreased and liver glycogen increased. A smaller group conform to the published findings of Best, the liver fat increased, and we have found also a concurrent increase in the liver glycogen. This latter finding is an exception to the rule of the reciprocal relationship between liver fat and glycogen.

Preliminary Report Concerning a Ballistocardiograph. An Analysis of the Record Obtained Under Various Physiologic and a Few Clinical Conditions. ISAAC STARR, A. W. RAWSON and H. A. SCHROEDER (Departments of Research Therapeutics, Pharmacology, and the Johnson Foundation, University of Pennsylvania). The study of the motion imparted to the suspended body by the recoil from cardiac action and the impact from the expelled blood dates from Yandell Henderson's experiments in 1904. Since then Heald and Tucker (1922), Angenheister and Laue (1928), and Abramson (1933) have published records These records show chiefly the normal form of the curve obtained, the effect of respiration, and of exercise. Our results are similar. The few clinical records published by Abramson are uninforming.

Our instrument consists of a light wooden bed rigidly braced with iron. This is suspended by wires from the ceiling and braced from the lateral wall to limit motion to the longitudinal direction. This bed is held, a little off its low point, by means of a strong steel cantilever spring. A lever, mirror, and optical system magnify the spring's motion about 1000 times at the recording camera. The curve obtained is not

dependent on the spring's period which is more rapid than any of the physiologic waves recorded.

To secure a ballistocardiogram the subject lies on the bed with his feet pressed firmly against a foot plate. Steel weights are added to make the total weight on the bed 200 pounds.

The normal record consists of a brief movement headward (pre-ejection phase) followed by a sharp movement feetward (recoil from ejection), a sharp movement headward (impact from blood striking the arches, head, etc.) and a final movement feetward (impact of blood striking lower portions of body, the wave having previously reached the upper parts). A small wave occurs constantly in diastole, probably due to the motion of the blood filling the heart.

Study of the records of 140 normal subjects at rest and more than 2 hours after a meal shows the following: The average total amplitude per square meter body surface of males is constant from 20 to 45 years of age and then steadily declines in the later decades of life. In women, this function is almost as great as in men at ages between 15 and 25, but it then declines, leveling out after the 25–35 decade to rejoin the declining men's curve at about 55 years.

If one uses the average wave amplitude, per square meter body surface, times mean blood pressure, or this amplitude times blood pressure times pulse rate, the age and sex differences mentioned above still hold. It seems obvious that the normal standards will not be a simple linear relationship.

The ballistocardiogram of cases of heart disease may differ from the normal by diminished amplitude, by abnormal form, or by both.

The auricular wave in cases of block can be clearly seen. The arrhythmias are easily recognized.

Several intraventricular conduction defects have been shown by notching of waves or by doubling of peaks. The one case of acute cardiac infarction examined showed a most abnormal record suggesting ventricular asynchronism.

The records of many cases of hypertension, without known cardiac weakness, have shown an abnormally low amplitude. This has also been found in the one case of neurocirculatory asthenia studied.

Abnormalities have been encountered which have no counterpart in the electrocardiogram or in any other method of cardiac examination.

Microscopic Observations on Extraendothelial Cells of Blood Capillaries. E. R. Clark and Eleanor Linton Clark (Laboratory of Anatomy, University of Pennsylvania). The development and behavior of extraendothelial or adventitial cells on small blood-vessels have been studied by prolonged microscopic observation of living vessels as seen in transparent chambers installed in the rabbit's ear, with the following results:

Adventitial cells form from fibroblasts or fibroblast-like cells which, in their migration, come in contact with and flatten out on the outside of the capillary wall. This process occurs chiefly during active new formation of blood capillaries—many capillaries receiving adventitial cells even before circulation through them has been established.

At first, they are sparsely and somewhat irregularly distributed on capillaries, have their long axis parallel with the capillary, and manifest slight powers of amœboid movement, which gradually subsides.

The further development of these outside cells depends upon the fate of the capillary, which may continue as a capillary, become part of an artery or vein, or retrogress. If it remains a capillary, the number of adventitial cells usually remains unchanged, although there may be an occasional increase in number by mitotic division. If it becomes part of an arteriole the number of cells increases rapidly—in part, at least, if not exclusively—by mitotic division of cells already present, until, by the end of not more than 6 days, there may be a continuous layer of outside cells; meanwhile the axis of the cell changes from longitudinal to transverse. If it becomes part of a venule, the number of cells increases somewhat, and the axes of a majority of the cells remain longitudinal. Around larger venules there may be a development of a capsule-like network from surrounding connective tissue. If a capillary retrogresses the adventitial cell is left behind in the tissue as an apparently inert, small cell, whose fate has not been followed.

If an artery diminishes in size, reduction in the number of outside cells occurs.

The adventitial cells on capillaries and small venules have shown no evidence of contractility. On arteries and arterioles, definite contractility develops in the transverse cells which have become smooth muscle cells, providing a vasomotor nerve has reached them. Such contractility may be manifested in arterioles which are 9 days old, as described in a previous article.

It is suggested that the term "Rouget" cell be given up, and, in its stead, the name "adventitial" cell be substituted—a return to the term "cellules adventices" employed by Rouget.

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